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Updates to the ACR Recommendations for treatment of RA; another step on a long road

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The development of targeted biologic therapy for rheumatoid arthritis (RA) has revolutionized treatment of this chronic disease and provided clinicians with a diverse menu of options for improving disease control, limiting radiographic progression of joint damage, and enhancing physical function. However, many fundamental questions about the optimal treatment of RA remain unanswered. What is the best initial DMARD therapy for patients with recent onset RA? What is the most effective treatment strategy for reducing long term damage? When should partially effective therapy be changed? How can the risks of drug therapy be mitigated for the individual patient? It is also difficult to translate our knowledge about the efficacy and safety of different therapies to the individual patient. Without validated biomarkers of treatment response, decision-making lacks a probability framework for predicting efficacy and toxicity at a 'personalized' level. For this reason, treatment decisions are guided by clinical intuition in the 'real world' despite being solidly grounded in a body of scientific evidence.

In this issue of *Arthritis Care and Research*, J. Singh and colleagues have taken the most current evidence from clinical studies to update the recommendations for the use of disease-modifying anti-rheumatic drugs (DMARDs) and biologics in RA (1). The last set of ACR recommendations for the treatment of RA was published in 2008 (2). In the short span of the past 4 years, the playing field has changed with the approval of new biologics and the publication of additional clinical information about the existing agents. The 2012 recommendations reflect a synthesis of the best available evidence in providing rheumatologists with an update on the important topic of RA treatment.

The investigators updated the 2012 recommendations using the same methodology as the 2008 recommendations. This approach utilized a Core Expert Panel (CEP) and a Task Force Panel (TFP), including an updated systematic review of the scientific literature. The CEP, which was comprised of individuals with clinical and methodologic RA-related expertise, was charged with developing clinical scenarios to address specific treatment issues. These scenarios were then rated by the TFP, a body of internationally recognized expert clinicians, methodologists in evidence-based medicine, and patient representatives. The ratings by the TFP were based on the updated evidence report and scored using the RAND/UCLA Appropriateness method (3). The treatment scenarios were then re-rated after extensive in

person discussion of the first round of ratings to develop consensus. If a majority of the expert panel could not agree on a single recommendation, then the rating was scored as "uncertain" and no recommendation was made. A formal recommendation by the panel required a median ranking score of 7 to 9 on the 9 point RAND/UCLA "appropriateness" scale. The strength of evidence supporting each recommendation was also assigned a value based on the widely used methods from the American College of Cardiology (4). Accordingly, a treatment recommendation with "A" level evidence was based on results from multiple randomized clinical trials, the highest quality evidence. A recommendation based on "B" level evidence came from a single randomized trial or non-randomized studies; and a recommendation derived from "C" level evidence was based on consensus opinion of experts, case studies, or standards of care. Notably, much of the evidence applied to the development of these recommendations was rated at the "C" level. However, this scale is non-linear and only provides a crude measure of the strength of the evidence. It is important to realize that a median score of 7 to 9 for any particular scenario, which leads to a formal recommendation, may embody a substantial difference of opinion by a minority of panel members. Moreover, the Rand/UCLA Appropriateness methodology does not explicitly require a certain level of evidence to produce a recommendation because it largely depends on the votes of experts. While the experts are presumably well schooled in the relevant scientific literature, their votes are also influenced by their scientific and clinical backgrounds as well as inherent biases. These limitations in the incorporation of clinical evidence and expert opinion are not unique to the rheumatic diseases and apply generally to the current state of guideline development across diseases and specialties. These issues also emphasize the importance of having of a transparent link between the recommendations and the strength of the underlying evidence. This transparency will improve with the ACR's adoption of the methods from the GRADE Working Group (5,6).

The 2012 update provides recommendations for the treatment of RA as well as key issues of patient care related to safety. While some of the recommendations are straightforward and well supported by evidence from the scientific literature, many are based on 'B' and 'C' levels of evidence and may change in the future with further study. Treatment recommendations are divided into those for patients with early RA (<6 mos) and those with established disease. The 6-month time point marking the border between early and established disease is consistent with the 2008 RA guidelines. This boundary between early and established disease takes into account the clinical presentation of disease and does not necessarily apply in any pathophysiologic sense. Greater understanding of disease pathogenesis and additional clinical data may lead to a different definition of early disease in the future. The recommendation to target low disease activity or remission in patients with early RA is a significant addition to the 2012 recommendations. It emphasizes the importance of early disease control in preventing irreversible joint damage and preserving long term function. This recommendation underscores the need to accurately assess RA disease activity and make timely adjustments in therapy based on this assessment. Rheumatologists have several measures of disease activity that are validated for clinical use (Table 3) and are further described in another article published in this issue of the journal (insert ref TBD, new #7.). The availability of multiple effective agents for RA provides the

clinician many options for adjusting therapy to achieve the goal of low disease activity and clinical remission.

DMARD monotherapy is recommended for disease of low, moderate or high activity in patients with early disease lacking poor prognostic factors. The panel also considered DMARD combination therapy to be an appropriate option in early RA for patients with high disease activity. The presence of poor prognostic factors (including functional limitation, extra-articular disease, seropositivity or erosions) alone in early RA was also believed to be an appropriate indication for the use of combination DMARD therapy. Some readers may disagree with this recommendation based on the fact that some patients in the poor prognostic category may respond favorably to DMARD monotherapy. A TNF inhibitor, with or without methotrexate (excepting infliximab), is also recommended for patients with high disease activity. For established RA, the panel made recommendations for initiating and switching traditional DMARDs and targeted biologics in several common situations. Decision points for a change in therapy were based on the inability to achieve at least mild disease activity. Flow chart diagrams are included in this update that help to simplify and clarify these recommendations. However, we know that the flow chart does not accurately depict the complexity of the medical decision-making process. Indeed, the results from clinical trials that provide much of the evidence for these recommendations only represent a “snap-shot” in time for any individual patient with RA.

The updated recommendations also address important safety issues, including use of biologic therapies in high-risk patients and vaccination for patients starting or currently receiving DMARDs or biologics. Vaccination recommendations are expanded beyond those presented in 2008. The recommendations for vaccination in the setting of DMARD and biologic therapies are presented in Table 5 of the article and will be of practical use to clinicians. However, additional questions remain in this area. For example, the panel was not able to make specific recommendations about the use of biologics in RA patients with a past history of hepatitis B virus infection. Additional clinical data are needed to clarify the safety of DMARDs and biologics in this population and more information is needed to guide interpretation of the serological results from viral hepatitis screening. Another important area of controversy is the use of biologics in patients with a history of malignancy. Only “C” level evidence was available for any of the considered scenarios. The resulting recommendations reflect a limitation of the case scenario based method. The panel recommended that starting or continuing any indicated biologic is appropriate in RA patients with a history of treated solid malignancy or non-melanoma skin cancer more than five years in the past. On the other hand, rituximab is recommended as appropriate for the treatment of RA in patients with this history within the past five years. Rituximab is also recommended for the treatment of RA patients who have a history of treated melanoma or lymphoproliferative malignancy. The authors appropriately note that little is known about the effects of biologic agents in patients with a recent history of malignancy because such patients are generally excluded from clinical trials. Moreover, no studies address the question of recurrent cancer risk in any systematic fashion. Most of the information about the cancer question comes from extrapolating long term safety data in patients without RA taking rituximab, where it has been used to treat lymphoproliferative malignancies, particularly lymphoma. While we agree that rituximab may be an appropriate choice for the

treatment of RA in the setting of a recently treated malignancy, it is premature to conclude that rituximab does not increase the recurrent cancer risk in this situation. The difficulty in making broad recommendations about safety in patients with a history of cancer is illustrated by the experience with the use of anti-TNF agents in RA patients, where long term monitoring experience exceeds that for rituximab. Here the safety monitoring data only points to an increased risk of non-Hodgkin's B cell lymphoma in adults and T cell lymphoma in children (8,9,10). Although these data suggest these agents may not be the best choice for patients with history of lymphoma, they do not tell us much about the risk of recurrent cancer. A recent study found that with the exception of malignant melanoma, the stage and prognosis of cancer which arises during treatment with anti-TNF agents was not worse than that of biologic-naïve RA subjects (11). Furthermore, large epidemiologic studies do not suggest an increased incidence of solid cancers from treatment with anti-TNF agents (12). Thus, based on our current knowledge, anti-TNF agents may be contraindicated with a history of some malignancies and not for others. We simply do not have enough data to make an informed decision in this instance. For this reason, a discussion between the doctor and the patient is essential communicating our lack of understanding about the risks of cancer recurrence in this situation.

Yet even high quality level 'A' evidence from controlled clinical trials does not eliminate all of the problems in applying treatment guidelines to individual patient decisions. Data derived from typical clinical trials may not reflect the experience of the average RA patient because only those with the most active disease and a limited number of co-morbidities are included in these study populations. Short duration clinical trials also do not provide adequate safety data over the long term. Thus, the opinion of the expert brings added value to the process by integration of experience across a wide range of patients. The formal approach used to adopt these and other ACR guidelines seeks to maximize the value of this expert opinion by accepting recommendations based on broad agreement among experts, while rejecting those lacking consensus support. However, experts also harbor biases from their own clinical experiences and interpretation of the literature that affect their voting on the scenarios. The RAND/UCLA approach attempts to strike a balance that depends on both published clinical data and expert opinion. In the face of a large body of clinical information of widely varying quality, the use of a rigorous, standardized approach that includes a comprehensive, critical review of the literature is essential. This update of ACR RA treatment guidelines uses such an approach, reflecting the importance and value that is placed on quality and validity in the development of all ACR guidelines. The authors are also to be congratulated on their efforts to make these guidelines relevant for many patients with RA and to address frequent decision points that will be applicable in most clinical settings.

The treatment of RA is a rapidly changing field with new therapies regularly coming on line and increasing focus on the development of novel strategies for achieving and sustaining clinical remission. It is likely that as this field evolves, some of these recommendations will need to be modified and updated to reflect this new information. The ACR must be nimble in keeping these recommendations as current as possible, and to continue to employ the best methods for assessing the available evidence. The ACR has embarked on a major and important road to provide rheumatologists with sound, evidence-based guidance for the

management of rheumatic disease. The 2012 RA treatment guidelines represent another step down this road.

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