Strategies for treating rheumatoid arthritis: new guidelines from the ACR

"The guidelines proposed by Saag et al. *reveal a considerable shift in the development process for guidelines and in the treatment of RA."*

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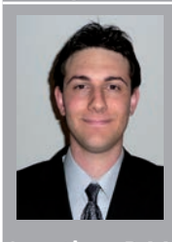

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What is a clinical guideline? Traditionally, a clinical guideline is known as a protocol designed to be an aid for guiding practitioners through critical decisions regarding diagnosis, treatment and management of a specific condition, shaped by both tradition and select specialists. Modern medicine with the introduction of evidence-based philosophy, has facilitated the evolution of guidelines to recommendations, taking into account the exponentially expanding quantity of literature, as well as the uniqueness of individual patients. ACR presents practice recommendations as the culmination of scientific research, trial-based evidence and expert opinion to the practicing clinician. These recommendations allow each physician to consider recommended approaches while making treatment decisions for their individual patients.

In June 2008, Saag *et al.*, as selected by the ACR, published the third set of recommendations for the treatment of rheumatoid arthritis (RA), focusing solely on the use of nonbiologic and biologic DMARDs. The mission was to create a series of recommendations on five areas set by the ACR:

- Indications for use
- Screening for TB (biologic DMARDs only)
- Monitoring for side effects
- Assessing the clinical response
- Including relative cost and patient preference in treatment choice (biologic DMARDs only)

Importantly, the utilization of a systematic literature review of the current body of literature and the use of a formal group process marks a divergence from the previous RA recommendations/guidelines from the ACR.

Recommendations within the five ACR prespecified areas were first molded through a rigorous review of published literature by a core expert panel consisting of clinicians and methodologists. These preliminary recommendations were then voted upon using specific patient scenarios, and were refined by a multidisciplinary task force panel (TFP) utilizing a modified Research and Development/University of California at Los Angeles (RAND/UCLA) appropriateness method (see Figure 1 of [1]). This TFP consisted of internationally recognized clinicians, methodologists and patient representatives with expertise in biologic and nonbiologic DMARDs, patient preference and healthcare economics. Revised recommendations were then subjected to review by ACR subcommittees, as well as the standard journal peer review process.

The recommendations presented by Saag *et al.* are focused on nonbiologic and biologic DMARD therapy exclusively in RA patients starting or resuming DMARD treatment and receiving optimal anti-inflammatory pharmacological agents (e.g., nonsteroidal anti-inflammatory drugs and glucocorticoids) and nonmedical therapies (e.g., physical therapy). Recommendations regarding nonsteroidal anti-inflammatory drug therapy in RA are found in the ACR 'White Paper' published in August 2008, by the ACR *Ad Hoc* group [2]. The TFP made the early decision to restrict recommendations to ten of the most studied and tolerated DMARD therapies: five nonbiologic (hydroxychloroquine, leflunomide, methotrexate, minocycline and sulfasalazine) and five biologic (abatacept, adalimumab, etanercept, infliximab and rituximab).

Nonbiologic DMARDs

For reasons of simplification, the TFP only considered patients who had never previously been treated with nonbiologic DMARDs. In addition to monotherapy, four dual therapies and one triple therapy were assessed (see Figure 2 of [1]). In summary, both methotrexate and leflunomide monotherapy were recommended for all RA patients regardless of disease duration and activity (see Table 1 of [1]) and irrespective of poor prognostic features. Hydroxychloroquine or minocycline

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monotherapy was recommended for RA patients without poor prognostic indicators and low disease activity, with disease duration of 24 months or less, and less than 6 months, respectively. Sulfasalazine monotherapy was recommended for RA patients of all disease durations and disease activity states with few poor prognostic features.

Dual-DMARD combinations (e.g., methotrexate plus hydroxychloroquine, methotrexate plus leflunomide, methotrexate plus sulfasalazine and hydroxychloroquine plus sulfasalazine) were generally reserved for patients with moderate or high disease activity with varying combinations of duration and prognosis, although there were exceptions (see Figure 2 in [1] for details). Overall, nonbiologic agents, predominantly methotrexate, were regarded as the first-line of DMARD therapy considering the lack of efficacy with nonsteroidal anti-inflammatory drugs and glucocorticoids (intra-articular and oral), as well as non-medical interventions.

Biologic DMARDs

The TFP reviewed and formulated recommendations for three classes of biologic DMARDs: the anti-TNF-α agents adalimumab, etanercept and infliximab; the T-cell inhibitor abatacept; and the B-cell inhibitor rituximab (see Figure 3 of [1]). In early RA (< 6 months disease duration), anti-TNF-α therapy was recommended along with methotrexate for those patients with high disease activity. In addition, the TFP expressly recommended an anti-TNF-α agent plus methotrexate if high disease activity was evident for less than 6 months with features of poor prognosis, assuming cost and insurance issues were not prohibitive. Anti-TNF-α therapy, in those whose disease duration was 6 months or more, was recommended if previous methotrexate monotherapy or other nonbiologic DMARD combination therapies led to an inadequate response, or if they had at least moderate disease activity irrespective of poor prognostic features. The TFP did not specify if or when to switch to another nonbiologic DMARD or when to add a biologic DMARD to ongoing methotrexate therapy.

The TFP recommended T-cell inhibition (abatacept) for patients with moderate disease activity and B cell-inhibition (rituximab) for patients with high disease activity who had failed both single and combination nonbiologic DMARD therapies and had poor prognostic features. Finally, biologic DMARD combination therapies were not advised, as the literature has shown both a higher incidence of adverse side effects and no benefit.

Contraindications of biologic & nonbiologic DMARDs

Since 2002 ACR guidelines did not specifically address the contraindications of nonbiologic and biologic DMARDs [3], Saag *et al.* used clinical trials and observational study data to consider and refine those recommendations (outlined in Tables 2 & 3 of [1]). Briefly, the TFP advised that none of these agents be started or resumed in the face of active bacterial infection (including upper respiratory infections and skin infections), TB, herpes zoster infection or fungal infection. Hematologic and hepatic contraindications for the nonbiologics were the usual ones. The TFP advised that leflunomide, methotrexate and anti-TNF-α agents were contraindicated in patients treated for a lymphoproliferative disease within the last 5 years. Anti-TNF-α agents were also contraindicated in patients with moderate-to-severe heart failure. All nonbiologic and biologic DMARDs except hydroxychloroquine were contraindicated in patients with acute hepatitis B or C. In patients with chronic hepatitis B and C, relative contraindications were complex (see Table 2 of [1]).

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Neurologic contraindications were limited by a paucity of clinical evidence, but the TFP recommended that anti-TNF-α agents should not be used in the presence of multiple sclerosis or demyelinating disorders. Leflunomide, methotrexate and minocycline were felt by the TFP to be contraindicated in women planning for pregnancy or in those who are currently pregnant, and breastfeeding mothers were also cautioned against the initiation or resumption of these therapies.

Safety monitoring, risk surveillance & preventative immunizations

Updating previous ACR recommendations [4] on safety monitoring in nonbiologic DMARD therapy, the TFP was faced with a unique dilemma. Although a strong body of evidence exists linking the use of specific DMARDs to particular toxicities, the assignment of precise monitoring recommendations is balanced by concerns regarding excessive blood tests and physician visits. Therefore, recommendations made by the TFP on this issue relied heavily on expert consensus.

The TFP recommended a complete blood count, liver transaminase level testing and serum creatinine level testing at the initiation or resumption of biologic or nonbiologic DMARD treatment (see Table 4 of [1]). In addition, when starting or resuming methotrexate or leflunomide treatment, the patient should be screened for hepatitis B and C if risk factors are present. Moreover, patients starting hydroxychloroquine treatment should receive a complete ophthalmologic examination to screen for retinal toxicity.

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Influenza vaccination was recommended by the TFP for patients before the commencement of any DMARD treatment (see Table 5 of [1]). Furthermore, pneumococcal and hepatitis A and B vaccinations were recommended for patients before starting leflunomide, methotrexate, sulfasalazine (pneumococcal vaccination only) and biologic DMARDs if vaccinations were not current. The TFP advised against all live vaccines during biologic DMARD therapy. The TFP recommended monitoring complete blood count, liver transaminase levels and serum creatinine levels for patients using leflunomide, methotrexate and sulfasalazine every 2–4 weeks for the first 3 months of treatment, every 8–12 weeks for months 3–6 of treatment, and every 12 weeks for treatment over 6 months (see Table 6 of [1]).

TB screening in patients receiving biologic DMARDs

As proposed by the ACR, the TFP recommended routine TB screening in patients considered for biologic DMARD treatment by TB skin tests and chest radiographs, as dictated by the individual's risk factors (see Figure 4 of [1]). The panel also recommended the retesting of patients with newly developed risk factors or exposures.

Conclusion & future perspective

The guidelines proposed by Saag *et al.* reveal a considerable shift in the development process for guidelines and in the treatment of RA. Expert consensus shaped by clinical evidence continues to be the basis for treatment guidelines for individual patients. While the publication of detailed recommendations brings with it the risk of 'cookbook' style medicine, the physician's judgment and the uniqueness of each patient ultimately determine treatment, a position consciously taken by these recommendations. In addition, the TFP reviewed areas in which data were too sparse for clear evidence-based recommendations to be made, or where consensus was not readily achievable. Hence, there are no specific recommendations concerning adding or switching therapies. These important areas where recommendations have not yet been formulated represent opportunities for future research.

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