Treatment Recommendations for the Management of Axial Spondyloarthritis

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Abstract: Clinical practice guidelines aid clinicians in providing optimal care for their patients. Over the past decade, treatment guidelines have been published for ankylosing spondylitis (AS), but there are no evidence-based recommendations for the management of axial spondyloarthritis. In 2003, Canadian rheumatologists published treatment recommendations for AS, which have been subsequently updated. More recently, in 2011, the Assessment of SpondyloArthritis international Society and the European League Against Rheumatism published recommendations for the management of AS. SPondyloArthritis Research and Treatment Network proposes an American College of Rheumatology–led effort to develop treatment recommendations for axial spondyloarthritis.

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CLINICAL PRACTICE GUIDELINES

Clinical practice guidelines are recommendation statements from government or professional societies designed to aid clinicians in providing optimal care for their patients. Implicit in the development of these guidelines is the systematic review of the available evidence; however, interpretation of the evidence and how it is used in the generation of recommendation statements can be quite variable, leading to disparate guidance and confusion by practitioners. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group was formed in 2000 with the intent to standardize the process of assessing the quality of evidence and the strength of recommendations. According to GRADE (www.gradeworkinggroup.org), a clinical practice guideline should offer explicit recommendations for typical patients in specific clinical circumstances and be based on sound evidence.[1,2] In order to achieve a high-quality clinical practice guideline, the GRADE working group developed a detailed stepwise process that is designed to define how the quality of the evidence influences the recommendations (Table 1). Although having confidence in research contributes to confidence in clinical decisions, the evidence alone is never sufficient. The goal of the GRADE guideline development process is to make the panel's judgments and disagreements transparent.[1,2]

The guideline panel is responsible for making the recommendation statements for the guidelines and should consist of relevant stakeholders such as expert clinicians, researchers, policy makers and patients and/or patient advocates.[3] Their first role is to determine the scope of the questions to be addressed by the guideline. These questions should be clinically relevant and specific, achieved best using the Patient, Intervention, Comparator, Outcome, Setting and Timing framework for asking clinical questions. The questions should be inclusive of any recognized subgroups that may require unique interventions or have unique responses to interventions. Once the scope and questions are identified, specific patient-centered outcomes are determined. Choosing which outcomes to include is usually conducted by a diplomatic process such as a Delphi or nominal approach.[1] A Delphi approach would have all participants answer questionnaires in several rounds. After each round, a summary of the results is presented with rationale, and participants revise their answers independently until the group converges on a common set of opinions.[4] In a nominal approach, a smaller group of panel members discusses the options, with the opportunity to rank the options from the most to the least acceptable. Those options consistently ranked the highest would be considered the most critical and become the focus of the guideline.[4] Once the scope and specific clinical questions and outcomes have been identified, the available evidence is to be systematically obtained and reviewed in order to determine estimates of effect for each outcome of each question. This requires a comprehensive literature search of all relevant databases, a search of grey literature and solicitation of unpublished data from stakeholders such as the pharmaceutical industry. Types of studies and specific inclusion/exclusion criteria should be predetermined and, optimally, all studies should be dual reviewed by investigators to ensure completeness. All studies included in the report should then be assessed for risk of bias and graded accordingly.[5]

Methodological limitations from the study design can increase the risk of bias and reduce one's confidence in the results. These include randomization, allocation concealment, blinding, accounting for those lost to follow-up, not following an intention-to-treat protocol and failing to follow protocol such as stopping early for benefit or failing to report all outcomes.[1] As appropriate, meta-analysis should be conducted to allow an estimate of the overall effect size for each outcome followed by the determination of the strength of this body of evidence.[1] The strength of the body of evidence reflects one's confidence in the estimation of the effect size and includes the domains of the risk of bias, inconsistency, indirectness, imprecision and publication bias.

Inconsistency occurs when there are widely differing results across studies (heterogeneity). Indirectness refers to indirect comparison such as comparing intervention A to intervention B by using placebo-controlled trials of each but without any direct comparison studies. Indirectness can also refer to differences in populations, interventions and outcomes between studies and the scope of the guideline's clinical questions.[1] Imprecision occurs when there is a wide confidence interval around the estimate of effect and can occur when there are few patients or few studies.[1]

The GRADE working group uses high, moderate, low and very low to define the confidence in the estimation of effect (Table 2). Randomized clinical trials startat a high strength of

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TABLE 1. GRADE guideline development process

1	Form a guideline panel
2	Define the scope
3	Ask precise clinical questions
4	Determine the critical outcomes of interest
5	Summarize the evidence
6	Determine the confidence in the effect estimates
7	Determine the quality of the evidence for each outcome
8	Determine the strength of the body of evidence
9	Make recommendations
10	Determine the strength of each recommendation

Adapted from Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy 2009;64:669–77.

evidence, while observational studies start at a low strength of evidence. For each domain, the strength is reduced by 1 level for a serious limitation and by 2 levels for a very serious limitation and increased by 1 for a large effect size and by 2 for a very large effect size.[1] The higher the strength of the evidence, the more likely is a strong recommendation. The panel's responsibility, however, is to also consider the balance of benefits and harms (the larger the difference between the desirable and undesirable effects and the certainty around that difference, the more likely is a strong recommendation), patient values and preferences (the more certainty of similarity in values and preferences, the more likely is a strong recommendation, but the more variability or uncertainty, the more likely a weak recommendation is warranted) and resource implications and feasibility (the fewer resources consumed, the more likely is a strong recommendation).

Each panelist rates each proposed recommendation, deciding whether the desirable effects of adherence to a recommendation reflects the group's degree of confidence in that assessment (Table 3). By consensus, the final recommendations and strength of each are determined.[4]

CRA/SPARCC RECOMMENDATIONS FOR SPONDYLOARTHRITIS

The Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada (CRA/SPARCC) working group published treatment recommendations for spondyloarthritis (SpA) in 2003.[6] These were drafted by rheumatologists with special expertise in SpA, focused on the use of antitumor necrosis factor (TNF) alpha therapies, and based on a systematic review of the literature. In 2007, major reappraisal of the development process was incorporated into the update of these treatment recommendations, which addressed major limitations of previously published recommendations.[7] These included the lack of a structured approach, broad stakeholder input that included patient consumers and guidance for interpretation and implementation not only at the level of daily clinical practice but also in the formal development of health-care policy.

A newly developed systematic approach involving broad stakeholder input was undertaken. First, the development of the treatment recommendations followed the standard operating procedures for the elaboration, evaluation, dissemination and implementation of recommendations endorsed by the European League Against Rheumatism (EULAR) Standing Committee for International Clinical Studies Including Therapeutics.[8] The process also adhered to the checklist of recommendations in the Appraisal of Guidelines for Research and Evaluation instrument.[9] Second, a major emphasis of this development process was the drafting of a template for incorporating broad stakeholder input, particularly the views and preferences of patient consumers, which had not been incorporated into the EULAR template. Third, the process addressed ethical considerations under the category of implementation of treatment recommendations.

The process was directed by a steering committee comprising the SPARCC executive committee and representatives from the CRA, rheumatologists from academic and community-based practices including those with expertise in clinical epidemiology and pharmacoeconomics, patient consumers and a representative from the John Dossetor Health Ethics Center. A working document was drafted that included a referenced summary of the evidence-based data and the results of a needs assessment of Canadian rheumatologists aimed at evaluation of current standards of care for ankylosing spondylitis (AS) patients in Canada and approaches to diagnostic evaluation, familiarity with outcome measures and current treatment guidelines and identification of continuing education priorities.[10] Several issues were identified for further consideration under the headings of disease category according to different SpA subtypes, disease phenotype according to a broad phenotypic subdivision into axial versus peripheral inflammation, category of recommendation and target population.

This led to a preliminary draft of treatment propositions. The contribution of patient consumers to the treatment propositions was developed in 3 steps: (1) Twelve national standards for arthritis prevention and care were developed by the Alliance for the Canadian Arthritis Program in April 2006 as a consensus document following a landmark summit on Standards in Arthritis Prevention and Care in October 2005.[11] The standards detail the minimal acceptable levels for arthritis care and prevention, irrespective of residence in Canada, and constitute the basis for action plans developed in collaboration with government. Alliance for the Canadian Arthritis Program is an umbrella group with membership from a wide cross-section

TABLE 2. Strength of the body of evidence—confidence in the estimation of effect

High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of the effect

Adapted from Brozek JL, Akl EA, Alonso-Coello P, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy 2009;64:669–77.