The Canadian Rheumatology Association/ Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis: A National Multidisciplinary Stakeholder Project

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ABSTRACT. ***Objective.*** Development of treatment recommendations for arthritis has traditionally relied on the compilation of evidence-based data by experts in the field despite recommendations by various bodies for broad stakeholder input. Our objectives were: (1) To develop evidence-based treatment recommendations for the management of spondyloarthritis (SpA) in Canada that also incorporate the perspective of multiple stakeholders. (2) To generate a procedural template for the multidisciplinary development of treatment recommendations.

Methods. The process was directed by a steering committee comprising the SPARCC Executive, rheumatologists from academic and community-based practice, patient consumers, and a representative from the John Dossetor Health Ethics Centre. Guidelines established by EULAR and stipulated in the AGREE instrument were followed. First, a working document was drafted that included a referenced summary of the evidence-based data and the 12 national arthritis care standards developed by the Alliance for the Canadian Arthritis Program. Second, a Web-based survey was conducted among patient consumers to address the relevance to patients of 2 primary outcome instruments that assess the effectiveness of treatment. Third, a list of questions was generated for drafting propositions by the ethics consultant. A Delphi consensus exercise was then conducted.

Results. Consensus was generated on a final list of 38 treatment recommendations categorized under the subject headings of general management principles, ethical considerations, target groups, definition of target disease, disease monitoring, and specific management recommendations.

Conclusion. Using broad stakeholder input, we provide treatment recommendations to guide clinical practice and access to care for patients with SpA in Canada. (First Release Sept 15 2007; J Rheumatol 2007;34:2273–84)

Key Indexing Terms:
TREATMENT RECOMMENDATIONS SPONDYLOARTHRITIS CANADA

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The Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada (CRA/SPARCC) working group published treatment recommendations for spondyloarthritis (SpA) in 2003[1]. These were drafted by rheumatologists with special expertise in SpA, were focused on the use of anti-tumor necrosis factor-α (anti-TNF-α) therapies, and were based on a systematic review of the literature. Treatment recommendations for ankylosing spondylitis (AS) have also been reported by the Assessments in AS Working Group (ASAS)[2,3]. The first ASAS recommendations[2] were a consensus statement on the use of anti-TNF-α agents in AS and were generated by expert opinion following a Delphi consensus exercise[4] of ASAS members. These have been updated following a review of the recent literature and a mailed questionnaire to ASAS members[5]. The second ASAS recommendations addressed the management of AS from a broader therapeutic perspective[3]. Key proposition statements were developed based on expert opinion by 22 participants, of whom 20 were ASAS members and 2 were orthopedic surgeons. A Delphi technique was used to reduce these to a predefined final 10 propositions over 3 rounds of voting, although the rationale for limiting the number of propositions was not stated. An intervention-specific systematic literature search was undertaken to identify evidence for each specified intervention and published separately[6].

These recommendations were a major step forward in generating international consensus on the appropriate management of AS. They have been used by formularies and expert committees as a framework to draft eligibility and maintenance criteria for anti-TNF-α therapies. However, it was acknowledged that they constitute recommendations as opposed to guidelines[3] in recognition that clinical practice varies widely across international boundaries according to factors such as experience in the absence of evidence-based data, availability of resources, patient and societal expectations, and the influence of regional opinion leaders. The latter was highlighted in the Canadian Rheumatology AS Needs Evaluation and Practice Survey, conducted in 2005, which showed that 57.4% of Canadian rheumatologists cited consultation with local experts as the primary desired source of further information for managing patients with AS[7].

New guidelines for development of treatment recommendations call for a structured approach and emphasize the importance of incorporating patient input. The Appraisal of Guidelines for Research and Evaluation (AGREE) instrument for evaluation of guidelines includes an item that rates the degree to which patients' views and preferences have been sought[8]. Drug regulatory authorities and formularies have also stated the desirability of including patient input into the decision-making process[9]. Most importantly, patient organizations have explicitly stated the necessity to address the views of the patient consumer[10]. However, the mechanism by which this is best accomplished has not been well defined. That patient consumer organizations can play a prominent role in the development of healthcare policy in Canada is well exemplified by the development of the first national standards on arthritis prevention and care that were delivered to federal and provincial health ministers by the Alliance for the Canadian Arthritis Program (ACAP)[10].

Another major omission in reported treatment recommendations to date is also the lack of guidance for interpretation and implementation not only at the level of daily clinical practice but also in the formal development of healthcare policy, particularly by physicians who serve on formulary committees. In particular, treatment recommendations cannot be proposed that are divorced from the realities of fiscal restraints, which vary not only between countries but also between different jurisdictions within a country. In Canada, recommendations for access to therapeutics on public formularies are made by provincial expert committees convened by each Canadian province who report to the respective provincial minister of health. Physicians who serve on these committees inevitably face serious ethical challenges posed by the requirement for them to serve the public interest in an environment of fiscal restraint while upholding their ethical commitment to promote patient welfare.

These considerations emphasize the continuing necessity not only for national treatment recommendations but also for broad stakeholder input in the process that leads to consensus through a new procedural template. This has been implemented in this extensive update to the 2003 Canadian recommendations for the treatment of SpA. Our objective was not only to provide recommendations for routine clinical practice in Canada but also to promote the formulation of national health

policy strategies that will ensure access to appropriate treatment for SpA.

MATERIALS AND METHODS

A systematic approach involving broad stakeholder input was undertaken (Figure 1). First, the development of the treatment recommendations followed the standard operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT)[11]. We also adhered to the checklist of recommendations in the AGREE instrument[8]. 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 addressed in previous recommendations or incorporated into the EULAR template. Third, it was the consensus view of our working group that ethical considerations should constitute an essential component of our treatment recommendations. This was addressed under the category of implementation of treatment recommendations.

Steering group composition. The project was initiated by the Executive of SPARCC (DAG, RDI, WPM, PR), who assigned a chairperson (WPM). A steering group was convened that consisted of the SPARCC executive, 9 rheumatologists with special expertise in SpA from 7 Canadian provinces in

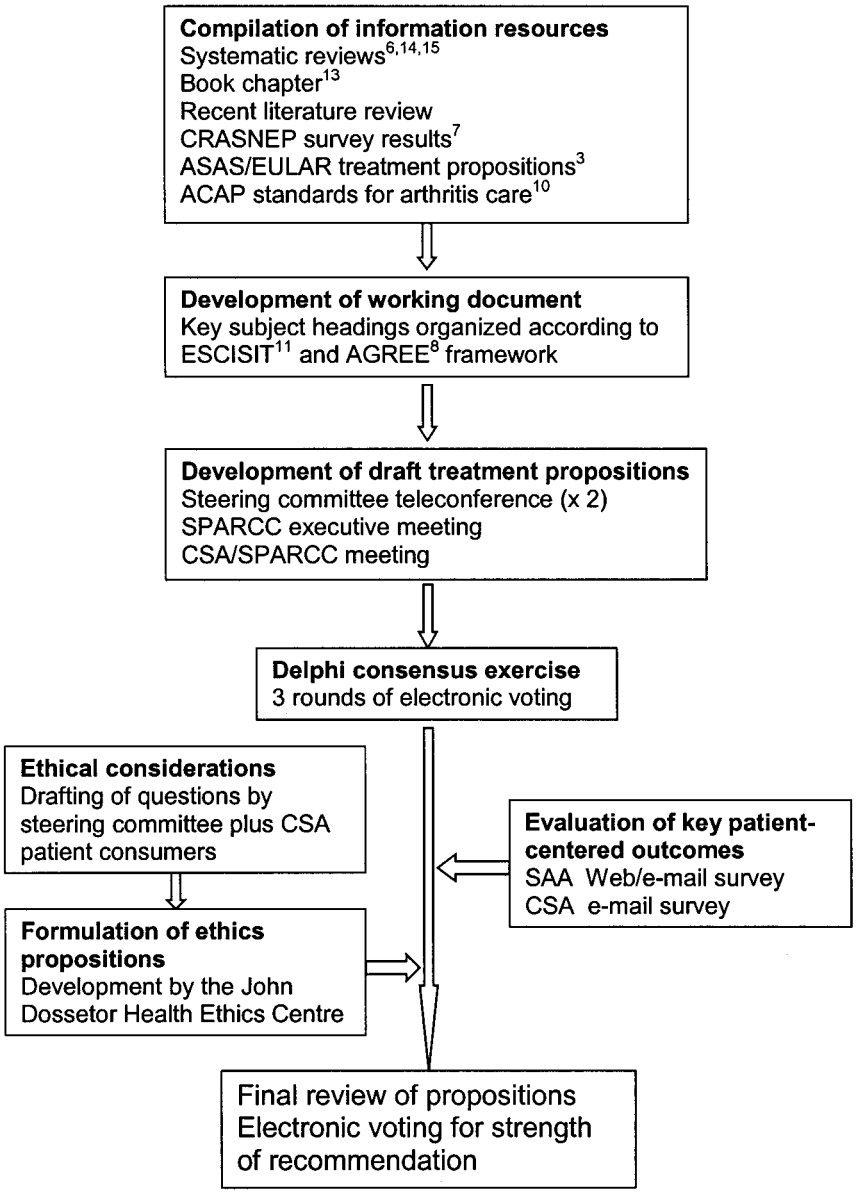

Figure 1. Development of the CRA/SPARCC treatment recommendations for SpA. ASAS: Assessments in Ankylosing Spondylitis International Working Group; EULAR: European League Against Rheumatism; CRASNEP: Canadian Rheumatology AS Needs Evaluation and Practice; ACAP: Alliance for the Canadian Arthritis Program; ESCISIT: EULAR Standing Committee for International Clinical Studies Including Therapeutics; AGREE: Appraisal of Guidelines for Research and Evaluation; SPARCC: Spondyloarthritis Research Consortium of Canada; CSA: Canadian Spondylitis Association; SAA: Spondylitis Association of America.

both community (n = 5) and academic based practices, a rheumatologist with special expertise in clinical epidemiology (PR), a rheumatologist with special expertise in the pharmaco-economics of SpA (AB), 2 rheumatologist representatives from the CRA, and 2 patient consumers from the Canadian Spondylitis Association.

Working document. A working document was drafted to ensure that as much information as possible was readily available at a single source. This included PDF documents of systematic reviews and book chapters. The working document was organized under the following headings:

A. Summary of the Canadian Rheumatology AS Needs Evaluation and Practice (CRASNEP) Survey[7]

The primary objective of this survey was to assess the current standards of care for AS patients in Canada. Secondary objectives included assessment of current approaches to diagnostic evaluation, familiarity with outcomes measures, familiarity with current treatment guidelines, and identification of continuing education priorities. It was drafted by a panel of 17 rheumatologists with a special interest in AS and incorporated the ASAS Working Group recommendations for outcome assessment and treatment. Eighty-six rheumatologists completed the survey out of 329 that were mailed.

B. Objectives of Treatment Recommendations

Several issues were identified for further consideration by the steering group under the headings of disease category, disease phenotype, category of recommendation, and target population. Clarification of the specific disease category that was being addressed by the treatment recommendations was done by considering the different subtypes of SpA, facets of SpA that might be considered defining characteristics, and approaches to diagnostic ascertainment. Prior treatment recommendations[1] and reports of individual clinical trials[12] have identified differences in response to therapeutic agents according to a broad phenotypic subdivision into axial versus peripheral inflammation highlighting this consideration in the development of treatment considerations for SpA. Group members were asked to consider whether this process would culminate in the development of treatment guidelines or recommendations and to identify the target populations toward whom the recommendations were directed.

C. Evidence-based Medical Literature

For AS, 2 extensive literature reviews have been published that were comprehensive in scope with respect to the range of treatment modalities examined, details of the search strategy, assignment of level of evidence, evaluation of outcome variables, and assessment of the magnitude of the treatment effect[6,13]. For psoriatic arthritis (PsA), 2 systematic reviews have been published that similarly evaluated the published literature on the management of axial[14] and peripheral[15] manifestations of PsA, respectively. These reports, together with data from abstracts and reports of clinical trials and observational studies published after these systematic reviews, were provided in the working document.

D. ASAS/EULAR Treatment Propositions for the Management of AS

The working document included both a PDF file of this report[3] as well as the 10 individual treatment propositions developed by the ASAS/EULAR working group.

E. Draft Treatment Propositions

A preliminary list of treatment propositions was drafted by the SPARCC Executive in March 2006 that was initially based on the ASAS/EULAR recommendations, evidence-based literature review, and the CRASNEP survey[7]. Additional propositions were added after the publication of the 12 national standards developed by ACAP in April 2006[10] and after development of propositions by the John Dossetor Health Ethics Centre that addressed ethical considerations in the implementation of treatment recommendations. The development of the first list of propositions followed 3 rounds of consultation among the steering group beginning with a teleconference in March 2006, a formal meeting at the inaugural Canadian Spondylitis Association in April 2006, followed by a second teleconference in May 2006. Evidence supporting the treatment propositions was categorized according to study design using a traditional hierarchy (A-D)[3]. The draft list of propositions was completed in June 2006 and then submitted to a Delphi consensus voting exercise.

Delphi consensus voting exercise. The development of the first list of treatment propositions was followed by 3 rounds of voting conducted electronically in which the steering group participants were asked either to rank order propositions from a range of related options for a particular category of treatment or to evaluate a specific proposition for inclusion or exclusion from the final list.

Where there were several options available for a specific category of treatment, those propositions that were ranked first by less than 40% of participants were deleted from subsequent rounds of voting. Propositions that were ranked first by at least 70% of participants in any round of voting were retained for the final list. If 3 rounds of voting did not succeed in the selection of a proposition as being ranked first by at least 70% of participants, that proposition was excluded.

Where only a single proposition was submitted for a specific treatment category, consensus for inclusion of that proposition was defined as a score $\geq$ 7 on a 0–10 numerical rating scale (NRS) by $\geq$ 70% of participants during any round of voting. Consensus for exclusion was defined as a score of $\leq$ 4 on the NRS by $\geq$ 70% of participants during any round of voting.

In the final vote, the group voted on the strength of recommendation (SOR) for each proposition according to a 0–10 NRS. This vote took place in November 2006.

Contribution of patient consumers. The contribution of patient consumers to the treatment propositions was developed in 3 steps:

A. Twelve national standards for arthritis prevention and care were developed by the ACAP in April 2006 as a consensus document following a landmark summit on Standards in Arthritis Prevention and Care in October 2005[10]. 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. ACAP is an umbrella group with membership from a wide cross-section of arthritis stakeholders, including patient consumer and professional organizations (ACAP members listed in Appendix 1). The steering group reviewed these standards and then proposed those that should be included in the draft treatment recommendations.

B. A Web-based survey evaluating the relevance of the primary questionnaires used to assess the symptoms and disabilities due to AS, i.e., the Bath AS Disease Activity Index (BASDAI)[16] and the Bath AS Functional Index (BASFI)[17] questionnaires, was conducted with the assistance of the Spondylitis Association of America (SAA). An e-mail invitation was sent to members of the latter organization with a weblink to the questionnaire. In addition, the survey was posted on the SAA website. The following question evaluated the relevance of the BASDAI: "Here is a questionnaire that arthritis specialists use to evaluate the symptoms that you may experience because of your disease. Please read through all 6 questions and then rate to what degree this questionnaire actually reflects those symptoms of your disease that have the greatest impact on your day-to-day life." The answer comprised a 5-point Likert scale from "completely includes the most essential symptoms" to " completely excludes the most essential symptoms." The following question evaluated the relevance of the BASFI: "Here is a questionnaire that arthritis specialists use to evaluate the impact of your disease on your ability to function using some common activities as examples. Please read through all 10 questions and then rate to what degree you feel these questions actually reflect your most essential disabilities in your usual day-to-day life." Responses were recorded on a 5-point Likert scale. Patients were also asked to indicate up to 3 of the most important symptoms and/or disabilities due to their disease not mentioned in the questionnaires. Additional symptoms and disabilities volunteered by patients were organized by the convenor (WPM) and a patient representative under main subject headings.

C. A presentation was given by the convenor (WPM) to patient representatives attending the inaugural meeting of the Canadian Spondylitis Association in April 2006. The presentation outlined the steps taken by the steering committee to develop the treatment recommendations. In addition, patients were asked to evaluate the relevance of the BASDAI and the BASFI using the same approach as described in "B." Patients were also asked to consider the ethical perspective on the formulation and implementation of treatment recommendations and to formulate questions for consideration by the John Dossetor Health Ethics Centre.

Ethical considerations. The steering committee drafted several questions for consideration by the ethics consultant from the John Dossetor Health Ethics Centre (LS) following discussion with patient representatives of the Canadian Spondylitis Association (CSA):

1. Is it ethical for physicians serving on a formulary committee to deny a listing on a public formulary, regardless of disease severity, for therapeutics shown to be effective when available therapies have failed?
2. Is it ethical for physicians serving on a formulary committee to deny a listing for such therapeutics when access on public formularies has been granted in other Canadian provinces?
3. What ethical considerations should dictate the recommendations of physicians serving on formulary committees?
4. How should physicians evaluate and use pharmaco-economic data in a manner that meets their ethical obligations to the patient?
5. If evidence supports superiority of one therapy or therapeutic regimen over another, is it ethical to require a therapy with an alternative because it is less expensive?

The consultant had free access to the working document and chose which of these questions should be examined further and/or whether additional questions ought to be considered. A series of draft propositions was formulated by the consultant and circulated among other members of the Centre for discussion. The final propositions were then sent for further consideration and discussion to the steering committee.

RESULTS

Selection of treatment propositions. The consultation process resulted in the drafting of an initial list of 57 propositions. The Delphi consensus voting exercise reduced the number of propositions to a final list of 38 organized under the following categories (Table 1):

A. General Management Principles

Two of the 5 propositions (3 and 5) selected by the group constitute 2 of the 12 national standards put forward by ACAP. One emphasizes the importance of incorporating patient preferences in prescribing treatment and regulatory decisions that affect access to treatment. Currently, formulary decisions on access to treatment are made by individual Canadian provinces, do not solicit input from patients, and have limited professional or public input. The consensus that this approach is no longer tenable is reinforced by the strength of recommendation for this proposition (SOR = 9.0). The second emphasizes the importance of post-approval surveillance. Although provincial formularies in Canada have emphasized the desirability of ongoing pharmacosurveillance, no province has developed systematic programs of surveillance for arthritis therapies, with the single exception of the Alberta Biologics Registry[18]. The necessity for change in healthcare policy is again highlighted by the strength of recommendation for this proposition (SOR = 9.0).

The proposal that treatment recommendations be organized according to primarily axial or axial with concomitant peripheral disease was largely influenced by the conclusions from 2 multicenter trials that evaluated salazopyrin therapy in SpA and showed benefit only in those with active peripheral disease[12,19]. However, this divergence in response between axial and peripheral manifestations of SpA has not been demonstrated in controlled trials of other systemic therapies for SpA, and studies in PsA have not evaluated axial manifestations[14]. The CRASNEP survey showed that most Canadian rheumatologists (> 80%) use second-line disease modifying antirheumatic drug (DMARD) therapies for AS, especially salazopyrin and methotrexate (MTX), primarily for the treatment of concomitant peripheral synovitis[7].

B. Ethical Considerations

The propositions developed under this category primarily attempt to clarify the roles and responsibilities of physicians that serve on formulary committees involved with implementation of these recommendations. Propositions 5 and 6 are of particular relevance to these recommendations because SpA is a complex group of disorders and formulary committees in Canada rarely include individuals with special expertise in the management of SpA. In addition, the experience of steering group members was that formulary committees across Canada vary considerably in the degree to which they solicit views from experts in the field.

C. Target Groups for Recommendations

The target groups selected by the committee reflect the current realities of healthcare delivery in Canada that is supported by both public and private payers. Consequently, the target groups included insurance payers, formularies, government agencies, and other healthcare providers in addition to rheumatologists.

D. Definition of Target Disease

Proposition 2 highlights the essential role of the rheumatologist in the diagnostic process and the importance of demonstrating radiological features of sacroiliitis according to current classification criteria[20]. In addition, it acknowledges recent work demonstrating the value of magnetic resonance imaging (MRI) as an additional imaging tool for the diagnosis of sacroiliitis through its ability to show inflammation in the sacroiliac joints and spine in the absence of structural changes indicating sacroiliitis[21]. However, the strength of recommendation was somewhat lower than for other propositions (SOR = 8.1) due to lack of familiarity with MRI by some committee members, lack of access to MRI in certain parts of Canada, and the fact that few studies have formally analyzed the sensitivity and specificity of standard MRI, particularly in early disease.

E. Disease Monitoring

The ASAS/EULAR recommendations specify the use of the

Table 1. CRA/SPARCC treatment recommendation propositions.

General Management Principles

1. Management recommendations for SpA should be organized under the categories of axial disease alone, axial with concomitant peripheral synovitis, and psoriatic SpA [defined according to CASPAR criteria (ClASsification criteria for Psoriatic ARthritis)]. Strength of recommendation (SOR): 9.3
2. Optimal management of SpA requires a combination of nonpharmacological and pharmacological treatments. (SOR: 9.8)
3. Patient preferences, including risk-benefit tradeoffs, must be incorporated into regulatory decision-making and prescribing of arthritis medications. (SOR: 9.0)
4. It is appropriate to consider pharmaco-economic data in formulating decisions on management strategies. The particular aim is to identify subgroups of patients with the highest predicted burden of disease for whom the additional benefits are worth the additional costs. However, economic considerations should not be decisive. (SOR: 8.5)
5. Postmarketing evaluation of new therapies for SpA should be implemented to ensure appropriate access and utilization of these agents, and to ensure their safety in an unselected population. (SOR: 9.0)

Ethical Considerations

1. A Formulary Committee, as a whole, has the duty to represent the public's interests in promoting the greatest health benefits possible (ethical principle of Beneficence) as fairly as possible within our limited shared resources (Justice), through an open and transparent process and in accordance with the best available evidence (Accountability). (SOR: 8.8)
2. Economic evaluations are often unduly limited, leaving out a clear analysis of the direct and indirect costs of suboptimal treatment. Ethically, suboptimal treatment is always questionable (principle of Nonmaleficence). (SOR: 8.2)
3. Fairness is required across all patient groups and illness categories. *Ad hoc* decisions that favor some groups but not others are not ethically acceptable. (SOR: 8.8)
4. The role of a physician on a Formulary Committee is to represent the medical profession's foundational Hippocratic commitment to promote patient welfare (Beneficence) and "above all else, to do no harm" (Nonmaleficence). No other professional or lay member of such a committee has this fundamental ethical commitment to patient well-being as their raison d'etre. While the facts of limited resources and the demands of justice must not be ignored, physicians participating on formulary committees have a special obligation to promote the best possible clinical options and, especially, to protect patients against the avoidable risks of suboptimal care. (SOR: 8.8)
5. Physicians are legally and professionally required to adhere to the accepted standards of clinical care, which in turn require all clinical decisions to be evidence-based. The role of a physician on formulary and other policy committees is thus to collect and interpret the available clinical and scientific data, and to educate the other committee members sufficiently to ensure fully informed decision-making by all participants. Where the physician lacks expertise regarding certain conditions or treatment options, they are duty-bound to consult clinical experts and represent the current standards of care accurately to the committee. Unlike any other professional on a policy committee, physicians bear the responsibility of ensuring that their fellow physicians are enabled to practice to the highest standard of evidence-based care. (SOR: 9.0)
6. The fact of resource limitations may require that qualifications be placed on access to some extremely expensive therapies. Physicians must be enabled to practice the highest standard of evidence-based medicine for the benefit of their patients, and thus even extremely expensive therapies that are clinically effective must not be excluded on principle. However, physicians need not rush to use the most resource-intensive options unnecessarily. Formulary committees should be encouraged to *work in conjunction with clinical specialists* to develop guidelines for access that promote safe and effective interventions at lower cost where possible, but that allow clinicians and patients to use necessary therapeutics when other options are not medically appropriate. (SOR: 8.6)
7. In a Canadian context, the delivery of healthcare is a provincial rather than federal duty. However, the principles of universality and comprehensiveness of the Canada Health Act, and the underlying ethical principle of Justice, indicate that treatments approved in one province should generally be available to patients in all provinces. Where additional evidence indicates that the treatment is not as safe or effective as previously believed, it may be appropriate to refuse funding for a therapeutic already accepted elsewhere. (SOR: 8.7)

Target Groups for Treatment Recommendations

1. These management recommendations are intended for (SOR: 9.0):
   a. Rheumatologists
   b. Insurance payers
   c. Other healthcare providers
   d. Government agencies
   e. Formularies

Definition of Target Disease

1. The primary defining features of spondyloarthritis are (SOR: 9.4):
   a. The presence of the HLA-B27 antigen
   b. The presence of sacroiliitis
   c. The presence of enthesitis
   d. The presence of spinal inflammation
   e. The presence of spinal ankylosis
   f. The presence of acute anterior uveitis
   g. The presence of dactylitis
   h. The presence of asymmetric large-joint arthritis
   i. The presence of psoriasis
2. Management recommendations for SpA should be based on the following criteria and/or diagnostic approaches (SOR: 8.1):
   Expert clinical evaluation by a rheumatologist and either a pelvic radiograph/computed tomography scan demonstrating unequivocal evidence of sacroiliitis or an MRI demonstrating unequivocal evidence of sacroiliac joint or spinal inflammation.

Table 1. continued.

Disease Monitoring

1. In general, treatment of SpA should be tailored according to (SOR: 9.5):
    a. Current manifestations of the disease (axial, peripheral, entheseal, extraarticular symptoms and signs)
    b. Level of current symptoms, clinical findings, and prognostic indicators
    c. Disease activity/inflammation
    d. Pain
    e. Function, disability, handicap
    f. Structural damage, hip involvement, spinal deformities
    g. General clinical status (age, sex, comorbidity, concomitant drugs)
    h. Wishes and expectations of the patient
2. The goals of treatment are to control pain and inflammation and prevent radiographic damage and disability. (SOR: 9.4)
3. Monitoring of patients with AS should include clinical variables (including questionnaires), laboratory tests, and imaging, all according to the clinical presentation. (SOR: 9.6)
4. Specific disease monitoring of patients with SpA in clinical practice should normally include (SOR: 8.8):
    a. Patient history
    b. BASDAI questionnaire
    c. BASFI questionnaire
    d. Patient global well-being
    e. Spinal mobility assessment
    f. CRP
    g. Toxicity
5. Participation in social, leisure, education, community, and work activities must be an integral measure used to evaluate outcomes by health professionals, educators, policy-makers and researchers. (SOR: 8.7)

Specific Management Recommendations

Nonpharmacological

1. Nonpharmacological treatment of SpA should include patient education and regular exercise. Individual and group physical therapy should be considered. Patient associations and self-help groups may be useful. Patient education and physical therapy should at some stage, preferably at diagnosis, be conducted in centers with special expertise in and facilities for managing SpA. Strength of evidence (SOE): A (SOR: 8.8)

NSAID and Analgesics

1. NSAID are recommended as first-line drug treatment for patients with AS with pain and stiffness. A sufficient trial of therapy should include at least 3 NSAID, each administered over a minimum 2-week period at accepted maximum dosage if tolerated. (SOE: A; SOR: 8.8)
2. When there is no therapeutic advantage, selective COX-2 inhibitor therapy should only be used in patients at increased gastrointestinal (GI) risk. In patients at risk who respond best to a traditional NSAID, a gastroprotective agent can be used. (SOE: A; SOR: 8.8)
3. Patients at high risk of serious GI adverse events due to NSAID, e.g., active inflammatory bowel disease, previous GI bleed, concomitant warfarin therapy, should receive alternative therapies as outlined below. (SOR: 9.4)
4. Analgesics, such as acetaminophen and opioids, might be considered for pain control in patients in whom NSAID are insufficient, contraindicated, and/or poorly tolerated, but these do not control inflammation and therefore should not replace NSAID. (SOE: C; SOR: 9.2)

Corticosteroids

1. Corticosteroid injections directed to the local site of musculoskeletal inflammation [sacroiliac joint (using fluoroscopy), peripheral joint, around painful entheses] may be considered (SOE: A). The use of systemic corticosteroids for axial or peripheral disease is not supported by evidence. (SOE: B; SOR: 8.8).

Disease Modifying Antirheumatic Drugs

1. There is no evidence for the efficacy of DMARD, including sulfasalazine and methotrexate, for the treatment of axial disease. (SOR: 8.9)
2. Sulfasalazine may be considered in patients with peripheral arthritis, including psoriatic and enteropathic SpA. Dosing should be up to 3 grams per day, if tolerated, over a period of 3 months and a complete blood count and liver enzyme investigations should be performed monthly. (SOE: A; SOR: 8.7)
3. Methotrexate may be considered in patients with peripheral arthritis, particularly psoriatic SpA, in a dose of up to 25 mg weekly, if tolerated, over a period of at least 3 months. A complete blood count should be performed monthly, and serum ALT, ALK every 2 months. Folic acid (1–5 mg daily) should be coadministered. (SOE: D; SOR: 9.0)

Anti-TNF Agents

1. Anti-TNF treatment should be given only under supervision by a rheumatologist to patients with persistently high disease activity despite conventional treatments. There is no evidence to support the obligatory use of DMARD before, or concomitant with, anti-TNF treatment in patients with predominantly axial AS. CRA recommendations for prevention of tuberculosis should be followed. (SOR: 9.4)
2. For patients with predominant axial disease, anti-TNF treatment should be offered to those with persisting symptoms despite a trial of NSAID therapy as defined above and evidence of active disease as defined by at least 2 of the following (SOE: A; SOR: 8.8):
    • BASDAI ≥ 4
    • Elevated CRP and/or ESR
    • Inflammatory lesions in the sacroiliac joints and/or spine on MRI

Table 1. continued.

3. For patients with concomitant peripheral arthritis, anti-TNF therapy should be offered to those with persisting inflammation (either synovitis or enthesitis) despite a trial of NSAID therapy as defined above and one DMARD (either methotrexate or salazopyrin). (SOE: A; SOR: 9.0)
4. Infliximab, etanercept, and adalimumab are all recommended for the treatment of SpA and choice of anti-TNF agent should be determined by consultation between the patient and doctor. (SOE: A; SOR: 9.5)
5. Appropriate dosing for etanercept is 25 mg twice weekly or 50 mg once weekly, for adalimumab 40 mg on alternate weeks, and for infliximab 3 mg/kg at 0, 2 and 6 weeks and every 8 weeks thereafter. The dose of infliximab can be increased to 5 mg/kg after 14 weeks if the clinical response is inadequate as defined below. For PsA the dose of infliximab is 5 mg/kg per infusion. (SOE: A; SOR: 9.0)
6. Maintenance on anti-TNF therapy should be based on attainment of a clinical response by 16 weeks. A clinical response is defined as either an absolute reduction of the BASDAI by 2 (0–10 scale) or a relative reduction of 50%. (SOR: 9.3)
7. Chronic reactive arthritis (ReA) that has proven resistant to NSAID treatment should follow the principles outlined for AS: anti-TNF agents for axial disease, and methotrexate or sulfasalazine for peripheral disease (SOE: D). The efficacy of antibiotic treatment for chronic ReA has not been proven. (SOR: 9.4)

Surgery

1. Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age. (SOR: 9.9)
2. Spinal surgery, for example, corrective osteotomy and stabilization procedures, may be of value in selected patients. (SOR: 9.7)

ASAS core set of outcomes. The CRASNEP survey indicates that rheumatologists in Canada are unfamiliar with the ASAS core set and so proposition 4 specifies the outcomes that are recommended by our committee. No consensus was reached on the frequency of monitoring. Proposition 5 is one of the 12 national standards put forward by ACAP to emphasize the importance of participation in society.

F. Specific Management Recommendations

The ASAS/EULAR proposition on the use of nonpharmacological therapies such as physiotherapy and patient education was adopted. Our recommendation for the use of NSAID defines an adequate trial of NSAID therapy as at least 3 NSAID, each given over a minimum 2-week period, and is based on current practice as revealed in the CRASNEP survey. This differs from prior recommendations that are less specific and based on expert opinion. Our recommendations also stipulate circumstances in which the risk for serious gastrointestinal (GI) events is sufficiently high that alternative therapies should be used. These include active inflammatory bowel disease, previous GI bleed, and concomitant warfarin therapy. The ASAS/EULAR propositions for the use of analgesics and corticosteroids were adopted with the modification that the use of systemic steroids for either axial or peripheral manifestations is not supported by evidence.

Our recommendations state that MTX may be an additional option for those with concomitant peripheral arthritis, particularly psoriatic SpA, although placebo-controlled randomized controlled trials in support of this proposition are limited to 2 studies of 58 patients[15]. Despite this, the committee considered it necessary to acknowledge the common use of this drug in clinical practice, as shown by the findings in the CRASNEP survey, where 85% of rheumatologists stated they would use MTX in doses of 20–25 mg weekly primarily for peripheral inflammation. Several additional DMARD were considered, such as leflunomide, cyclosporine, antimalarials, and gold, but none was selected by consensus voting.

There are several points of distinction between the ASAS/EULAR and the CRA/SPARCC recommendations with respect to the use of anti-TNF-α therapies. First, there was consensus that these agents should be given only under supervision by a rheumatologist. We also stipulate adherence to the CRA recommendations for the prevention of tuberculosis. Second, our recommendations state that for patients with concomitant peripheral synovitis failing a trial of NSAID therapy, a trial of DMARD therapy may include either salazopyrin or MTX. Third, our definition of active disease depends on the presence of at least 2 of the following 3 measures: (1) elevated C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR), (2) BASDAI ≥ 4, and (3) inflammatory lesions of the sacroiliac joints and/or spine on MRI. This conclusion was attained by a simple majority of votes (54%) as group members could not reach consensus (70%) as defined *a priori* with some members favoring a requirement for only one of the 3 measures (BASDAI ≥ 4), recognizing that MRI in a timely fashion is inaccessible in many parts of Canada. The counter-argument was that the BASDAI is subjective and correlates poorly with MRI-defined inflammation while acute-phase reactants are both insensitive and nonspecific. Although consensus on this issue was not attained, it was agreed prior to the final vote that the issue was of sufficient importance to warrant inclusion in the final draft of treatment propositions based on the results of a simple majority.

Since the publication of our first treatment recommendations it has been shown that adalimumab is an efficacious anti-TNF agent in the treatment of AS and psoriatic SpA[22,23]. Consequently, all 3 available anti-TNF-α agents are recommended for the treatment of the articular features of SpA. Dosing for etanercept and adalimumab is the same as for RA. It is recommended that infliximab be started at a dose of 3 mg/kg every 8 weeks, with dose escalation being considered only if the response is inadequate[24]. For psoriatic SpA there are no data evaluating a 3 mg/kg dose of infliximab and so the 5 mg/kg dose is recommended.

Contribution of patients. There were 639 respondents who accessed the Web-based patient survey through the SAA website (mean age 49.2 years, mean symptom duration 21 years) and 225 respondents who were members of the SAA who accessed the survey following e-mail notification (mean age 44.6 years, mean symptom duration 15.8 years). For website respondents, 34.4% and 51.5% reported that the BASDAI either completely includes or includes most but not all of the most essential symptoms, respectively (Table 2). For e-mail respondents, 37.5% and 45.1% reported that the BASDAI either completely includes or includes most but not all of the most essential symptoms, respectively. A majority (55.5% and 53.2% of Web and e-mail respondents, respectively) volunteered additional symptoms (> 5%) that were categorized under iritis/eye inflammation (18.9%), impairment of mobility (13.3%), sleep impairment (12.7%), chest/rib cage pain (12.5%), and bowel disorder (6.6%). For the BASFI, similar proportions of respondents reported that this questionnaire either completely includes or includes most but not all of their essential disabilities (Table 2). A smaller proportion (48.9% and 38.2% of Web and e-mail respondents, respectively) volunteered additional disabilities (> 5%) that were categorized under limitation in sitting (16.9%), walking (12.2%), driving (7.6%), personal care/hygiene (7.0%), lifting (6.5%), getting into/out of a car (5.7%), and impaired neck mobility (5.5%). Results of the voting by patient consumers belonging to the CSA were very similar (Table 2).

In conclusion, a consistent majority of patients (> 80%) rated the items in the BASDAI and BASFI as reflecting either all or most of their essential symptoms or disabilities experienced on a daily basis, and there were no major differences between the 3 different categories of patients. The steering committee therefore considers the inclusion of these questionnaires in the routine monitoring of patients as essential, with the proviso that there may be additional items that ought to be considered in future research.

DISCUSSION

It is our view that the process of developing treatment recommendations should emphasize the following 3 key components. First, there should be a systematic approach to the evaluation of the evidence-based medical literature as outlined in the standard operating procedures developed by EULAR[11]. Second, there should be a mechanism for incorporating the views of individual patients as well as patient organizations. Third, there should be a mechanism for addressing the clinical practice realities of the local environment, which includes current standards of clinical practice, particularly where the evidence–based literature does not address an essential aspect of management, availability of healthcare and economic resources, and societal values on access to healthcare. Only the first component can and should be addressed by international treatment recommendations, which then serve as a preliminary step for the development of treatment recommendations in individual countries where a broader array of stakeholders should be included.

Our recommendations differ from the international ASAS/EULAR recommendations in the following respects. They are broader in scope since they address psoriatic, reactive, and enteropathic SpA. We considered this appropriate because it is our consensus that the literature and clinical practice support the view that the same treatment recommendations are appropriate for axial SpA regardless of the specific clinical SpA subset. It is acknowledged, however, that there are no clinical trials that have specifically examined patients with only axial features of psoriatic, reactive, or enteropathic arthritis. To date, trials of biologic agents in AS have largely utilized the modified New York criteria for the classification of AS as the primary inclusion criterion. Thus, these studies included patients with PsA, enteropathic, and reactive arthritis, and subgroup analyses have not demonstrated differential responses[25]. It is also our consensus that treatment recommendations for SpA should be presented primarily according to axial and peripheral manifestations of SpA because there is evidence supporting differences in response to DMARD. In particular, both salazopyrin and MTX have been shown to be efficacious in peripheral SpA, especially psoriatic disease, but lack efficacy for axial disease[15]. Our recommendations reflect the view of the large majority of Canadian rheumatologists surveyed in CRASNEP that 2 weeks is a sufficient period of time to assess the efficacy of an NSAID in SpA and that failure of 3 NSAID should require reevaluation of the management strategy. This is supported by clinical trial data showing that symptomatic responses have plateaued by 2 weeks[26,27]. This differs from the ASAS/EULAR recommendations, which stipulate the use of a minimum of 2 NSAID over a 3-month period. Moreover, we stipulate circumstances where NSAID should not be used consistent with previous recommendations

Table 2. Results of a Web-based survey for patients to evaluate the relevance of the BASDAI and BASFI questionnaires to their essential symptoms and disabilities, respectively. Data are percentages.

	BASDAI					BASFI				
	1	2	3	4	5	1	2	3	4	5
Website respondents, n = 639	0.9	5.2	8.8	51.5	34.4	1.5	4.9	8.8	45.7	40.0
E-mail respondents*, n = 224	1.3	5.8	15.6	45.1	37.5	4.1	3.0	13.7	43.7	37.6
CSA, n = 13	0	0	15.4	46.1	38.5	0	0	15.4	46.1	38.5

* Members of the Spondylitis Association of America. CSA: Canadian Spondylitis Association.

developed by Canadian rheumatologists on the appropriate use of NSAID[28-30].

Our recommendations continue to support the use of MTX in patients with concomitant peripheral synovitis, although not in those with axial disease alone, as presented in the original SPARCC recommendations on the use of anti-TNF-α therapies[1]. We acknowledge that for AS there are few data to support its use, even in those with concomitant peripheral synovitis, although the CRASNEP survey shows that a large majority of Canadian rheumatologists use this agent to treat the peripheral inflammation of SpA. MTX is also mainstream therapy for psoriatic peripheral arthritis despite the lack of clinical trial data to support its use. It is relevant that all trials to date have examined doses that would be considered inadequate by clinical rheumatologists. For instance, none of the 3 controlled trials of this agent in AS reported to date has evaluated a dose higher than 10 mg weekly[7]. One open-label study reported in abstract form after the completion of our Delphi exercise describes 20 patients, of whom 7 had peripheral joint involvement, who received MTX 15 mg weekly for 4 weeks followed by 20 mg weekly for 12 additional weeks[31]. Although only 25% of patients were considered responders, a nonsignificant decrease in swollen joint count was noted from 4.7 at baseline to 1.2 at 16 weeks.

Our recommendations for the use of anti-TNF therapies also differ in several respects from prior recommendations. Since our first recommendations[1], adalimumab has been reported to be efficacious for both AS[22] and PsA[23] in pivotal phase III trials, and this is supported by MRI data from a placebo-controlled Canadian trial of AS[32]. Moreover, response rates as defined by the ASAS20, ASAS40, and ASAS5/6 composite measures in AS[22,33,34] and American College of Rheumatology 20% response (ACR20), ACR50, and ACR70 responses in PsA[23,35,36] are comparable for all 3 available anti-TNF-α agents in pivotal trials. Consequently, we conclude that all 3 agents have comparable efficacy for axial and peripheral joint inflammation in SpA. For infliximab, clinical trial data support only the use of the 5 mg/kg dose every 6 weeks for maintenance treatment of both AS and PsA. Interim data from a recent double-blind placebo-controlled Canadian trial evaluating the dose of 3 mg/kg every 8 weeks in AS confirm the findings of an open-label study supporting its efficacy at this lower dose[24,37]. Pharmacoeconomic evaluation using Canadian data indicates that the use of a 3 mg/kg dose for maintenance would be cost-effective in a Canadian setting[38]. We therefore recommend that infliximab be initiated in AS using 3 mk/kg and only escalated to 5 mg/kg from 14 weeks if the response is inadequate.

One issue that did not meet the consensus definition after 3 rounds of voting was the definition of active disease requiring anti-TNF-α therapy. A simple majority (54%) voted for 2 of the following 3 features: BASDAI ≥ 4, elevated CRP/ESR, and inflammatory lesions on MRI. The remainder preferred only one of the 3 features, specifically a BASDAI ≥ 4. It is relevant that the BASDAI has not been validated for criterion validity, correlates poorly with the CRP[39], and does not correlate at all with MRI features of inflammation[40]. It was also argued that acute-phase reactants lack sensitivity in AS, being elevated in only 40%–50% of patients[41]. With respect to a single activity-defining feature, there are concerns regarding access to MRI, lack of familiarity with interpretation of MRI features of AS on the part of both rheumatologists and radiologists, and insufficient data on sensitivity and specificity. Timely access to MRI is available in some Canadian provinces, however, and it was argued that MRI should be included if the purpose of treatment recommendations is to aim at achieving best practice.

The importance of including a mechanism for incorporating the views of both individual patients as well as patient organizations into the development of treatment propositions is highlighted in our findings that there are several major deficiencies in the assessment of outcomes and the implementation of treatment recommendations. For instance, although participation restriction has been put forward by ACAP as an integral outcome that should be assessed by physicians, no instruments have yet been developed to assess participation restrictions due to SpA. "Activities and Participation" comprises one of the 4 key components of the International Classification of Functioning, Disability and Health (ICF), which has been developed in order to define the full spectrum of the functional impact of disease in a more systematic way[42]. Preliminary data have now been reported that attempt to comprehensively address the limitations in functioning from the AS patient's perspective using an ICF checklist[43]. This information will be essential in drafting future treatment recommendations.

Patient consumers have definitively stated their desire to provide input into the process whereby treatment recommendations are implemented, but this has received scant attention to date. It seems intuitive that this is essential if adherence, both societal and at the level of individual patients, is to be attained. Although regulatory authorities cite the desirability of patient input into the decision-making process, none has proposed a mechanism. Moreover, the deliberations of Canadian formulary expert committees as well as the Canadian Common Drug Review have generally not been open proceedings, with little input from professionals or the public. The desirability of pharmacovigilance to obtain drug effectiveness and safety data in real-world practice has also been repeatedly cited in surveys of Canadian formulary committees, but few have developed systematic programs of pharmacosurveillance.

Ethical considerations in the drafting of treatment recommendations have also received scant attention to date, despite the increasing proliferation in costly therapies and the consequent strains on the finances of public formularies. We fully acknowledge the complexities of the issues raised by these propositions, but nevertheless feel compelled to state our con-

sensus position, not as a final solution but as a stimulus for further discussion in this important area.

In conclusion, we conducted a series of extensive consultations through face-to-face meetings, teleconferences, Web surveys, and electronic voting exercises over a period of 8 months that included a broad array of stakeholders to develop treatment recommendations for the management of SpA in Canada. It is our hope that the 38 propositions stated here will serve to assist rheumatologists in clinical practice in Canada, will provide guidance to health policy planners that will ensure access to appropriate treatment for patients with SpA, will serve as a procedural template for the development of treatment recommendations in general, and will stimulate further research and discussion of neglected issues raised in the conduct of our deliberations.

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APPENDIX

Alliance for the Canadian Arthritis Program, member organizations. Arthritis Community Research and Evaluation Unit; Arthritis Consumer Experts; Arthritis Health Professions Association; Arthritis Research Centre of Canada; Bone and Joint Decade; Canadian Arthritis Network; Canadian Arthritis Patient Alliance; Canadian Orthopaedic Association; Canadian Paediatric Rheumatology Association; Canadian Rheumatology Association Cochrane Collaboration; Consumer Advisory Council of the Canadian Arthritis Network; Consumer Advisory Board of the Arthritis Research Centre of Canada; Institute of Musculoskeletal Health and Arthritis; Patient Partners in Arthritis; The Arthritis Society

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