2014 Update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations

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ABSTRACT. ***Objective.*** The Canadian Rheumatology Association (CRA) and the Spondyloarthritis Research Consortium of Canada (SPARCC) have collaborated to update the recommendations for the management of spondyloarthritis (SpA).

Methods. A working group was assembled and consisted of the SPARCC executive committee, rheumatologist leaders from SPARCC collaborating sites, Canadian rheumatologists from across the country with an interest in SpA (both academic and community), a rheumatology trainee with an interest in SpA, an epidemiologist/health services researcher, a member of the CRA executive, a member of the CRA therapeutics committee, and a patient representative from the Canadian Spondylitis Association. An extensive review was conducted of literature published from 2007 to 2014 involving the management of SpA. The working group created draft recommendations using multiple rounds of Web-based surveys and an in-person conference.

Results. Recommendations for the management of SpA were created. Part II: Specific Management Recommendations addresses management with nonpharmacologic methods, nonsteroidal anti-inflammatories and analgesics, disease-modifying antirheumatic drugs, antibiotics, tumor necrosis factor inhibitors, other biologic agents, and surgery. Also included are 10 modifications for application to juvenile SpA.

Conclusion. These recommendations were developed based on current literature and applied to a Canadian healthcare context. It is hoped that implementation of these recommendations will promote best practices in the treatment of SpA. (First Release Feb 15 2015; J Rheumatol 2015;42:665–81; doi:10.3899/jrheum.141001)

Key Indexing Terms:
SPONDYLOARTHRITIS ANKYLOSING SPONDYLITIS PSORIATIC ARTHRITIS

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To address rapid changes in spondyloarthritis (SpA) management, the Canadian Rheumatology Association (CRA)/Spondyloarthritis Research Consortium of Canada (SPARCC) presents the 2014 Update of the CRA/SPARCC Treatment Recommendations for the Management of Spondyloarthritis. We aim to inform best practices of the Canadian rheumatologists, primary care physicians, allied health professionals, patients, and policy makers.

These recommendations have been divided into 2 parts: (Part I) Principles of the Management of SpA, and (Part II) Specific Management Recommendations. Part I addresses optimal SpA management in Canada and has been presented previously, and the principles were largely derived from expert opinion[1]. Part II contains specific recommendations for treatment with a larger body of literature support. Supplementary data are available online at jrheum.org.

Recommendations were based upon the highest quality of evidence available at the time of this review. They are intended to promote best practices and improve delivery of healthcare for those with SpA. Recommendations should not be interpreted as rigid or legal standards, nor are they intended to replace the clinical judgment of rheumatologists and other trained SpA healthcare providers acting according to the individual needs of the patient.

MATERIALS AND METHODS

Participants, patient population, scope, development process, evidence-based literature review, grading evidence, and extended review methodology have been described previously[1]. Table 1 reviews levels of evidence (LOE) and strength of recommendation (SOR).

RESULTS

The CRA/SPARCC Specific Management Recommendations are summarized in Table 2. These recommendations may be applied to juvenile SpA (JSpA) enthesitis-related arthritis (ERA) through modifications (Table 3). The LOE, SOR, and expert opinion score (EO) are listed for each recommendation. EO was evaluated on a 5-point Likert scale ranging from "disagree completely" to "agree completely". Barriers to implementation of individual recommendations are also described. These address elements of the healthcare system that may affect the applicability of the recommendations.

Specific Management Recommendations

Nonpharmacological

Recommendation 1. Treatment includes education, exercise, physical therapy (PT), and the involvement in patient associations. PT and exercise in ankylosing spondylitis (AS) have been the subject of systematic literature reviews, finding positive effects for both, with PT having the greatest effect (LOE I, SOR A)[2,3].

Systematic review of exercise in AS demonstrated small improvements in spinal mobility, but was limited by the poor quality of included studies (LOE II, SOR B)[4].

Involvement in patient organizations is based upon expert opinion (LOE IV, SOR D).

Barriers to implementation include lack of reimbursement for services and geographical limitations to access.

Recommendation 2. Recommends smoking cessation. Smoking is associated with worse radiographic outcomes in axial SpA (axSpA); further, this relationship may be dose-dependent[5,6]. Smoking has been associated with worse inflammation and radiographic damage in early axSpA, and with radiographic severity even in long-standing disease[7,8].

Smoking also harms patient outcomes, including the Bath Ankylosing Spondylitis Functional Index and functional status in both early and established SpA[7,9,10,11,12,13,14]. Again, this relationship may be dose-dependent[15]. Smoking also limits function in psoriatic arthritis (PsA)[16].

The LOE is II and SOR is B for smoking cessation in SpA.

There are no barriers to the implementation of smoking cessation recommendations.

Table 1. Custom system for assigning LOE and SOR.

LOE	SOR
I: Metaanalysis, systematic reviews of RCT, or an individual RCT	A: Strong recommendation: • Direct level 1 evidence
II: Metaanalysis, systematic reviews of observational studies (cohort/case control studies), or individual observational studies, OR RCT subgroup/posthoc analysis	B: Moderate recommendation: • Direct level 2 or extrapolated level 1 evidence
III: Nonanalytic studies (case reports, case series)	C: Weak recommendation: • Direct level 3 or extrapolated level 2 evidence
IV: Expert opinion	D: Consensus recommendation: • Expert opinion based on very little evidence
NR: Recommendation is not linked to evidence	

LOE: level of evidence; SOR: strength of recommendation; RCT: randomized controlled trial; NR: not reported.

Table 2. 2014 Update on the CRA/SPARCC Specific Treatment Recommendations for the Management of SpA.

Recommendation	LOE	SOR	EO
Nonpharmacological			
1. Nonpharmacological treatment of SpA should include patient education and regular exercise, preferably at centers of expertise or with experienced physiotherapists. Individual and group physical therapy should be considered. Patient associations and self-help groups may be useful.	I (physio) II (exercise) I (education) IV (self-help)	A (physio) B (exercise) A (education) D (self-help)	5.0
2. Smoking contributes to radiographic progression in axSpA, and smoking cessation should be recommended.	II	B	5.0
NSAID and analgesics			
3. NSAID are recommended as first-line drug treatment for symptomatic patients with axSpA. A sufficient trial of therapy is defined as at least 2 NSAID, each administered over a minimum 2-week period at the maximum tolerated dosage, unless contraindicated.	I	A	4.9
4. The decision to use NSAID should be made after considering the patient's cardiovascular risk factors. NSAID with the best cardiovascular safety profile should be preferred.	I	A	4.9
5. When there is no therapeutic advantage, selective COX-2 inhibitor therapy should be used in patients at increased risk for GI adverse events. In patients at risk who respond best to a traditional NSAID, a gastroprotective agent can be used.	I	A	4.7
6. Patients on longterm, regular NSAID therapy should be regularly monitored for changes in GI, cardiovascular, and renal status.	I	B	4.7
7. If NSAID are insufficient or contraindicated, alternative pain control strategies (i.e., acetaminophen, opioids) should be considered. It should be noted that non-NSAID analgesics do not control inflammation.	IV	D	4.9
Corticosteroids			
8. Corticosteroid injections at local sites of inflammation (i.e., SI joints, peripheral joints, and entheses) may be considered.	I (SI joints) II (PsA joint) IV (all other sites)	A (SI joints) B (PsA joint) D (all other sites)	4.7
9. Short courses of systemic corticosteroids may be considered for specific manifestations. The sustained use of systemic steroids is not recommended or supported.	I (AS) IV (other SpA)	A (AS) D (other SpA)	4.7
DMARD			
10. There is no evidence for the efficacy of DMARD, including SSZ and MTX, for the treatment of axSpA.	I	A	4.8
11. SSZ, MTX, and leflunomide may be considered in patients with peripheral SpA, but have only minimal to moderate evidence of efficacy. Dosing and monitoring of these drugs should be tailored to the individual patient and follow usual standard of care.	I	A	4.9
12. Combination therapy with DMARD should be considered in peripheral SpA, particularly in patients with poor prognostic features, moderate–high disease activity and in patients with recent-onset disease. Combination therapy should also be considered in patients with inadequate response to monotherapy.	IV	D	4.4
Antibiotics			
13. A trial of rifampin plus either doxycycline or azithromycin may be tried for 6 mos in cases of proven post-*Chlamydia* chronic reactive arthritis. There is no evidence of efficacy for antibiotics in axSpA.	IV	D	4.5
TNFi			
14. TNFi should be given only under supervision by a rheumatologist to patients with persistently high disease activity, despite other therapy. Routine laboratory screening (complete blood count, liver and renal function) as well as screening for Hepatitis B and C (and HIV in high risk patients) should be performed prior to initiation. Screening for latent TB infection should be performed prior to initiation. Baseline ANA may be considered. CRA recommendations for prevention of TB should be followed. Seasonal vaccination for influenza is recommended for patients before or during treatment with TNFi. Hepatitis B vaccine should be considered in high-risk groups in patients determined to be nonimmune to HBV. H. zoster vaccine should be considered in patients aged 60 yrs or older.	IV	D	4.9
15. There is no evidence to support the obligatory use of DMARD before, or concomitant with, TNFi in patients with axSpA.	I	A	4.8
16. For patients with predominantly axSpA, TNFi should be offered to those with persistent symptoms after a trial of NSAID therapy as defined above and evidence of active disease as defined by at least 2 of the following: • BASDAI > 4 • Elevated CRP or ESR • Inflammatory lesions in the SI joints and/or spine on MRI	I (TNFi efficacy) IV (active disease definition)	A (TNFi efficacy) IV (active disease definition)	4.2

Table 2. Continued.

Recommendation	LOE	SOR	EO
17. For patients with predominantly peripheral SpA, TNF inhibitors should be offered to those with persistent inflammation despite a trial of NSAID as above and 1 DMARD.	I (TNFi efficacy) IV (post NSAID and DMARD)	A (TNFi efficacy) D (post NSAID and DMARD)	4.9
18. For patients with refractory enthesitis or dactylitis, TNFi should be offered to those with persistent inflammation.	I (enthesitis) II (dactylitis)	A (enthesitis) B (dactylitis)	4.5
19. Several TNFi are available for the treatment of SpA, including infliximab, etanercept, adalimumab, golimumab, and certolizumab. The choice of TNFi should be determined by consultation between the physician and patient. Dosing and monitoring of these drugs should be tailored to the individual patient and follow usual standard of care.	I	B	5.0
20. Maintenance on TNFi should be based on attainment of clinical response 16 weeks after initiating treatment. In axSpA, a clinical response is defined as either an absolute reduction of the BASDAI by 2 (0–10 scale) or a relative reduction of 50%. In peripheral SpA, a clinical response is defined as a reduction in active joint count by 30%.	IV	D	4.7
21. The choice of TNFi should incorporate the presence or absence of extraarticular manifestations. When possible, the chosen TNFi should treat both SpA and the particular extrarticular manifestations effectively.	I	A	4.9
22. Combination of MTX and TNFi does not influence clinical efficacy, though in peripheral SpA it may be associated with prolonged drug response.	II	B	4.5
23. Nonresponders to TNFi may benefit from switching to another TNFi.	II	B	4.9
Other biologic agents			
24. Rituximab may be considered for the treatment of axSpA for patients in whom TNFi are contraindicated.	II	B	4.2
25. Ustekinumab may be considered for the treatment of patients with SpA with concomitant moderate to severe cutaneous psoriasis.	I	A	4.8
26. There is currently no evidence for the use of other biologic agents in SpA, including ABA, TCZ, and anakinra.	II (ABA) I (TCZ) II (anakinra)	B (ABA) A (TCZ) B (anakinra)	4.9
Surgery			
27. Total hip arthroplasty should be considered in patients with refractory pain or disability and radiographic evidence of structural damage, independent of age.	II (axial) IV (peripheral)	B (axial) D (peripheral)	5.0
28. Spinal surgery, for example, corrective osteotomy and stabilization procedures, may be of value in selected patients, ideally at surgical centers with experience in AS spinal disease.	III	C	4.8

CRA: Canadian Rheumatology Association; SPARCC: Spondyloarthritis Research Consortium of Canada; SpA: spondyloarthritis; LOE: level of evidence; SOR: strength of recommendation; EO: expert opinion; axSpA: axial SpA; NSAID: nonsteroidal antiinflammatory drugs; COX-2: cyclooxygenase-2; GI: gastrointestinal; SI: sacroiliac; PsA: psoriatic arthritis; AS: ankylosing spondylitis; DMARD: disease-modifying antirheumatic drugs; SSZ: sulfasalazine; MTX: methotrexate; TNFi: tumor necrosis factor inhibitors; HIV: human immunodeficiency virus; TB: tuberculosis; ANA: antinuclear antibody; HBV: hepatitis B virus; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MRI: magnetic resonance imaging; ABA: abatacept; TCZ: tocilizumab.

Nonsteroidal Antiinflammatory Drugs (NSAID) and Analgesics

Recommendation 3. NSAID are first-line drug treatments for symptomatic patients with axSpA. An appropriate trial consists of at least 2 NSAID, each administered over a minimum of 2 weeks at maximum tolerated dosage, unless contraindicated.

Several randomized controlled trials (RCT) and posthoc analyses have demonstrated NSAID efficacy in AS in the long and short terms[17,18,19,20,21]. A metaanalysis of NSAID RCT showed a medium–large effect size for pain, function, and patient assessment of the disease[22]. NSAID may have the greatest effect in patients with AS who have elevated acute-phase reactants (APR)[23].

Continuous NSAID may modify radiographic outcome in AS. An RCT of continuous versus on-demand celecoxib found that continuous users had less radiographic progression, even after adjusting for confounders[24]. Posthoc analysis demonstrated that this effect was restricted to those with elevated APR[25]. The GErman SPondyloarthritis Inception Cohort found no difference in radiographic progression with high NSAID intake overall, but less progression in those with baseline syndesmophytes and elevated C-reactive protein[26].

The LOE for Recommendation 3 is I and SOR is A.

There are no barriers to implementation of this recommendation.

Recommendations 4-6. Address potential toxicities and methods to minimize adverse events from NSAID use. A literature review for these recommendations is beyond this article's scope, but are addressed in a 2008 review paper[27]. The LOE and SOR for recommendations 4 and 5 are I and A, and for 6 they are I and B.

There are no barriers to the implementation of these recommendations.

Recommendation 7. Acetaminophen and opioids may be

Table 3. The 2014 Update on the CRA/SPARCC Treatment Recommendations for the Management of SpA for application to JSpA(ERA).

Recommendation	LOE	SOR
Nonpharmacological		
1. Children and adolescents with JIA have reduced aerobic fitness, but can participate in exercise without disease exacerbation. Patients with JSpA(ERA) should be strongly encouraged to participate in regular physical activities that are compatible with the child's general abilities and development.	I	B
2. Peripheral arthritis and enthesitis involving the foot and ankle are common in JSpA(ERA) and the use of comfortable, cushioning, and supportive foot orthotics should be considered in these patients.	I	B
NSAID and analgesics		
3. Peripheral SpA is more common in JSpA(ERA) and should be managed with an adequate trial of NSAID (1–2 mos) initially.	IV	D
4. Sacroiliitis in JSpA(ERA) can be managed according to the axSpA recommendations.	IV	D
Corticosteroids		
5. No specific modifications.	I	B
DMARD		
6. No specific modifications.	I (SSZ) III (MTX, LEF)	A (SSZ) C (MTX, LEF)
Antibiotics		
7. No specific modifications.	IV	D
TNFi		
8. TNFi are beneficial in JSpA(ERA) and should be prescribed in accordance to the predominantly axial or peripheral SpA recommendations. TNFi available for the treatment of JSpA(ERA) is currently restricted to ETN, ADA, and IFX.	I (IFX, ADA) II (ETN)	A (IFX, ADA) B (ETN)
Other biologic agents		
9. The use of these agents in JSpA(ERA) has not been studied.	IV	D
Surgery		
10. No specific modifications.	IV	D

CRA: Canadian Rheumatology Association; SPARCC: Spondyloarthritis Research Consortium of Canada; SpA: spondyloarthritis; JSpA: juvenile SpA; ERA: enthesitis-related arthritis; LOE: level of evidence; SOR: strength of recommendation; JIA: juvenile idiopathic arthritis; NSAID: nonsteroidal antiinflammatory drugs; axSpA: axial SpA; DMARD: disease-modifying antirheumatic drugs; SSZ: sulfasalazine; MTX: methotrexate: LEF: leflunomide; TNFi: tumor necrosis factor inhibitors; ETN: etanercept; ADA: adalimumab; IFX: infliximab.

tried in patients with otherwise uncontrolled pain. To our knowledge, no trials address this issue (LOE IV, SOR D).

There are no barriers to the implementation of this recommendation.

Corticosteroids

Recommendation 8. Consider corticosteroid injections at sites of inflammation, including sacroiliac (SI) joints, peripheral joints, and entheses. Placebo-controlled trials of radiographic-guided SI joint injections showed significant improvements in pain with minimal adverse events[28,29,30,31,32]. One study was contradictory[33]. Computed tomography–guided SI injection decreased magnetic resonance imaging (MRI) inflammation[31,32]. Case series also supported SI joint injection[28,34,35]. The LOE and SOR for SI joint injection are I and A.

One prospective cohort study of intraarticular steroid injection in PsA demonstrated good response at 3 months[36]. No studies assessed intraarticular injections in other SpA, nor were there studies of entheseal injection. (LOE II, SOR B for intraarticular corticosteroid injection in PsA. LOE IV, SOR D for all other intraarticular or entheseal injections.)

A limitation to implementation of this recommendation is the difficulty of accessing radiographic-guided SI joint injections.

Recommendation 9. Consider a short course of systemic corticosteroids for specific manifestations of SpA, though sustained use is discouraged. An RCT of oral steroids in NSAID-resistant AS found high-dose prednisolone over 2 weeks was effective[37]. Interestingly, low-dose prednisolone was ineffective, contrary to prior practice of using steroid-responsiveness to discriminate mechanical from inflammatory back pain[37]. Two additional small studies have supported the use of pulse methylprednisolone in NSAID nonresponders[38,39]. Systemic corticosteroid use in PsA was historically discouraged owing to the concern of psoriasis flare, but low-dose corticosteroid use in PsA may be common[40]. The LOE and SOR of a brief course of systemic steroids in AS are I and A; and for all other SpA, IV and D.

There are no barriers to the implementation of this recommendation.

Disease-modifying Antirheumatic Drugs (DMARD)

Recommendation 10. There is no evidence for DMARD efficacy in axSpA.

A systematic review of methotrexate (MTX) for AS concluded there was "no evidence to support any benefit of MTX in the treatment of AS"[41].

Sulfasalazine (SSZ) use in AS was also reviewed, showing reduction of morning stiffness and erythrocyte sedimentation rate (ESR), but no effect on pain, function, mobility, or enthesitis[42,43,44]. SSZ was compared head-to-head with etanercept (ETN) in the axSpA ASCEND (Ankylosing Spondylitis Study Comparing ENbrel and Sulfasalazine Dosed Weekly) and ESTHER (Enbrel Sulfasalazine Early Axial Spondyloarthritis) trials[45,46]. Though SSZ did improve some axial symptoms, ETN produced significantly greater improvements than SSZ[45,47]. ESTHER demonstrated that SSZ decreased MRI inflammation in axSpA, but minimally compared to ETN[46]. These studies lacked placebo control, affecting the ability to derive decisive conclusions regarding SSZ effectiveness in axSpA.

Two studies showed that leflunomide (LEF) was ineffective in active AS[48,49].

Overall, Recommendation 10 is LOE I, SOR A.

There are no barriers to the implementation of this recommendation.

Recommendation 11. Addresses DMARD use in peripheral SpA based upon PsA data. DMARD use in PsA was recently extensively reviewed, and metaanalysis concluded that MTX was effective for peripheral arthritis[50]. Significant improvements were found in joint counts[51,52,53], pain[51,53], and ESR[52,53]. However, MTX did not affect radiographic progression[54]. Subsequently, a double-blind, placebo-controlled RCT of MTX 15 mg/week showed that MTX did not improve joint counts, APR, or patient-reported outcomes (PRO)[55].

The above metaanalysis assessed SSZ use in peripheral PsA and found it to be effective, but minimally so[50]. SSZ also did not prevent radiographic progression[56].

Effectiveness of LEF in PsA was also assessed[50]. A placebo-controlled RCT found LEF useful for peripheral arthritis and psoriasis[57]. Open trials have supported these results[58,59]. An observational study showed that LEF improved joint counts, dactylitis, and PRO[60].

Overall, the LOE and SOR for the use of DMARD such as MTX, SSZ, and LEF in peripheral SpA (specifically peripheral PsA) are I and A. Our scoring metric assigns high levels to metaanalyses and RCT, regardless of potential flaws in study design. The effect of these DMARD, though positive, is clinically minimal.

Recommendation 12. Consider combination therapy with DMARD in peripheral SpA, particularly those with poor prognostic factors, greater disease activity, recent-onset disease, and monotherapy resistance (LOE IV, SOR D).

Recommendations 11 and 12 may be restricted in circumstances where patients have limited drug coverage.

Antibiotics

Recommendation 13. Consider testing antibiotics in post-*Chlamydia* chronic reactive arthritis (ReA). A review of antibiotics for ReA concluded that their effects were, in general, uncertain[61]. The regimen proposed for post-*Chlamydia* ReA is based upon 1 double-blind placebo-controlled trial. Followup studies to confirm these findings have not yet been performed. In view of the findings of the recent metaanalysis, the LOE is IV and the SOR for this recommendation is D[62].

Significant barriers to implementation include often limited access to diagnosing physicians, and high drug costs.

Tumor Necrosis Factor Inhibitors (TNFi)

Recommendation 14. Addresses administration, monitoring, and preventive measures that are suggested when prescribing TNFi in SpA (LOE IV, SOR D).

There are no barriers to the implementation of this recommendation.

Recommendation 15. No evidence supports the DMARD use before or concomitant with TNFi in axSpA, as reviewed in Recommendation 12 (LOE I, SOR A).

There are no barriers to the implementation of this recommendation.

Recommendation 16. TNFi are efficacious for axSpA. This details the clinical characteristics of patients suitable for treatment. A metaanalysis encompassing 2005–2009 concluded that evidence for treatment with TNFi was very high, and found TNFi were similarly effective in nonradiographic axSpA and AS[63].

There has been extensive reporting of the effectiveness, safety, and reduction of MRI inflammation for each TNFi approved for axSpA in Canada: infliximab (IFX)[64,65,66,67,68,69,70,71,72,73,74], ETN[45,46,75,76,77,78], adalimumab (ADA)[79,80,81,82,83,84,85,86,87,88,89], golimumab (GOL)[90,91,92,93,94], and certolizumab pegol (CZP)[95,96].

A prospective study also suggested that earlier TNFi treatment in AS reduced radiographic progression[5].

The LOE and SOR for TNFi in axSpA are I and A.

Recommendation 16 also states that TNFi should be offered to those with persistent active axSpA despite NSAID treatment. These recommendations define active axial disease as the presence of 2 of the following: Bath Ankylosing Spondylitis Disease Activity Index > 4, elevated APR, or the presence of inflammatory lesions in the SI joint and/or spine on MRI. This definition of active disease is based on expert consensus; therefore, this portion of Recommendation 16 has an LOE IV and SOR D.

The major barrier to the implementation of this recommendation is drug cost. Even those privately insured may face a large co-payment. Patients may face lengthy application processes for drug access.

Recommendation 17. For peripheral SpA, offer TNFi to those with persistent inflammation despite a trial of NSAID and 1 DMARD. This recommendation is derived from PsA literature.

A review of PsA literature up to July 2011 included studies of IFX, ETN, ADA, and GOL[97]; all demonstrated TNFi efficacy in ACR composite outcomes and skin manifestations[97]. No studies specifically addressed TNFi use in psoriatic oligoarthritis[97]. A metaanalysis encompassing 1962–2010 and including studies of IFX, ETN, and ADA also supported these findings and demonstrated that TNFi repressed radiographic progression in PsA[50].

ADA has also been shown to improve outcomes in non-AS, non-PsA peripheral SpA[98].

TNFi use in peripheral SpA has an LOE I and SOR A. Recommendation 17 also advises that TNFi be used in those with persistent inflammation despite a trial of NSAID and 1 DMARD. This component of the recommendation is based on expert opinion (LOE IV, SOR D).

Cost remains the largest barrier to this recommendation's implementation. Some patients may endure severe disease while waiting to fulfill public reimbursement criteria.

Recommendation 18. Consider TNFi treatment for unresponsive enthesitis and dactylitis. Two studies found TNFi were efficacious for enthesitis[99,100]. TNFi effect on enthesitis has been assessed as a secondary outcome by numerous PsA RCT, all demonstrating improvement[97]. No RCT directly addresses dactylitis treatment with TNFi, but a cohort study of PsA showed that TNFi treatment may be a predictor of improvement[101]. Dactylitis is frequently a secondary outcome in PsA RCT of TNFi[97]. IFX[102,103], ETN[104], ADA[105], GOL[106,107], and CZP[108] improved dactylitis. The LOE and SOR for TNFi for enthesitis are I and A; for dactylitis, II and B. Patient characteristics for TNFi treatment are based on expert opinion (LOE IV, SOR D).

The major barrier to implementation of this recommendation is cost.

Recommendation 19. Many TNFi are available, including IFX, ETN, ADA, GOL, and CZP. Choice of TNFi is based upon mutual understanding between physician and patient. There are no head-to-head trials of TNFi, but a similar study design in Phase III RCT supports comparable efficacy (LOE I, SOR B).

There are no barriers to the implementation of this recommendation.

Recommendation 20. Defines clinical response to TNFi in both axial and peripheral SpA. These recommendations are consistent with current recommendations from the Assessment of Spondyloarthritis international Society and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, but are based on expert consensus (LOE IV, SOR D)[21,109].

There are no barriers to the implementation of this recommendation.

Recommendation 21. TNFi choice should incorporate treatment of extraarticular manifestations. Several TNFi are licensed for extraarticular manifestations, including plaque psoriasis (IFX, ETN, ADA), Crohn's disease (IFX, ADA), and ulcerative colitis (IFX, ADA, GOL)[110]. Treatment of uveitis with TNFi is off-label, but may influence drug choice. The LOE is I and the SOR is A for this recommendation.

Use of TNFi for the treatment of uveitis is currently off-label, and cost remains the largest barrier to implementation[110].

Recommendation 22. There is no evidence that combining MTX with TNFi improves efficacy, but it may affect persistence in peripheral SpA. In AS, addition of MTX to IFX did not affect outcomes, infusion numbers, TNFi switching, or dosing[111,112,113,114,115]. In PsA, RCT demonstrated clinical and radiographic efficacy of several TNFi regardless of concomitant MTX[102,106,116,117,118]. However, observational studies and registries of PsA demonstrated that combining MTX with TNFi improved persistence[119,120]. The LOE and SOR for MTX in addition to TNF for efficacy are I and A; for treatment persistence in peripheral SpA, II and B.

There are no barriers to implementation.

Recommendation 23. TNFi nonresponders may benefit from TNFi switching. To our knowledge, no RCT has studied TNFi switching in AS, but numerous observational studies, registries, and retrospective studies support switching[121,122,123,124,125,126]. Switching has also been studied in PsA observational studies and registries[127,128,129]. CZP has been found to be effective in patients with PsA who have previously failed TNFi[108]. In overall SpA, response to second and third TNFi was high[130]. The Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases study also showed response to switching, though there was less retention of the second agent[131]. This recommendation has a LOE II and SOR B.

Implementation may be limited because of therapy cost.

Other Biologic Agents

Recommendation 24. Consider rituximab (RTX) in axSpA when TNFi are contraindicated. RTX is a monoclonal antibody against CD20+ B cells. One trial demonstrated that established, TNF-naive patients with AS were able to achieve clinical response to RTX while TNFi failures were unresponsive[132]. A registry of RTX in SpA also demonstrated moderate efficacy in TNFi-naive subjects[133]. Recommendation 24 has an LOE II and SOR B.

However, RTX is currently not approved for SpA treatment in Canada[110]. Cost is another barrier.

Recommendation 25. Consider ustekinumab (UST), a monoclonal antibody against interleukin 12/23, for SpA with concomitant moderate–severe psoriasis. The PSUMMIT-I RCT found significant improvements in clinical outcomes and good safety with UST[134]. A

double-blind RCT of patients with PsA and ≥ 3% body surface area psoriasis also showed that UST reduced arthritis, enthesitis, dactylitis, and skin lesions, and improved function[135]. UST was also found to reduce progression of radiographic damage in PsA[136]. The LOE and SOR for this recommendation are I and A. UST is approved for PsA treatment in Canada[110].

Though UST has been approved, it does not appear on the provincial formulary universally. Cost is also an obstacle.

Recommendation 26. There is no evidence for the use of other biologics in SpA, including abatacept (ABA), tocilizumab (TCZ), and anakinra[137,138,139,140,141,142,143,144,145,146,147,148]. Interestingly, a 6-month, randomized, double-blind, placebo-controlled study of ABA in PsA suggested that it may be effective at a dose of 10 mg/kg, potentially indicating a differential effect in peripheral versus axial disease[137]. As more data about non-TNFi biologics continue to emerge, the authors anticipate ongoing rapid change in this area. Currently, the LOE and SOR for ABA, TCZ, and anakinra are II and B, I and A, and II and B, respectively.

There are no barriers to the implementation of this recommendation.

Surgery

Recommendation 27. Consider total hip arthroplasty (THA) in patients with pain, disability, and damage, regardless of age. THA in AS has been studied through registries and case series[149,150]. Observational studies of THA in AS have shown good outcomes, even when performed at a young age[151,152,153,154,155,156,157,158,159,160,161,162]. The LOE and SOR for this recommendation are II and B. No studies exist of THA in peripheral SpA (LOE IV, SOR D).

Barriers to implementation include long waiting lists and access to specialized surgical centers.

Recommendation 28. Studies of spinal surgical interventions in SpA are largely case series showing positive effects (LOE III, SOR C)[163,164,165,166,167,168,169,170,171,172,173,174,175,176]. A detailed review of these surgical procedures is beyond the scope of this paper. Recommendation 28 has LOE III and SOR C.

The major barrier to the implementation of this recommendation is the limited access to specialized surgical centers.

Juvenile SpA

JSpA typically presents with more peripheral and entheseal involvement compared with adults[177]. It includes several overlapping subtypes: juvenile ankylosing spondylitis (JAS), juvenile PsA, reactive arthritis, enteropathic arthritis, and undifferentiated disease called ERA[177]. Currently, ERA is the most common form of SpA seen among children with juvenile idiopathic arthritis (JIA)[177] and the recommendations will address this population specifically. Because of shared familial and genetic predispositions, JSpA(ERA) may be thought of as an on-a-continuum-of disease with adult SpA[177]. Indeed, many adult rheumatologists in Canada will manage patients with JSpA(ERA) who have passed the age of 18. This section of the 2014 Update of the CRA/SPARCC Recommendations for the Management of SpA will address adaptations of the adult SpA recommendations that may be applied to JSpA(ERA).

Nonpharmacological

Recommendation 1. Physical activity is encouraged in JSpA(ERA). Though patients with JIA have reduced aerobic and anaerobic fitness[178,179], participation in exercise does not exacerbate disease[180]. Single-blind RCT of exercise in JIA also showed improved function and quality of life[181,182]. Note that these studies do not specifically assess exercise in JSpA (LOE I, SOR B).

There are no barriers to the implementation of this recommendation.

Recommendation 2. Peripheral arthritis and enthesitis involving the foot and ankle are common. Use of foot orthotics is supported by a randomized trial that may have included patients with ERA, but did not specifically address JSpA(ERA). The LOE is I and the SOR is B[183].

Implementation of this recommendation may be limited because of cost.

NSAID and Analgesics

Recommendation 3. Peripheral arthritis is more common in JSpA(ERA). Patients should be treated with a longer NSAID trial (1–2 mos; LOE IV, SOR D).

There are no barriers to the implementation of this recommendation.

Recommendation 4. Sacroiliitis in JSpA(ERA) can be managed with NSAID according to the adult axSpA recommendations. To our knowledge, no trials in JSpA(ERA) exist (LOE IV, SOR D).

There are no barriers to the implementation of this recommendation.

Corticosteroids

Recommendation 5. There are no modifications. Only 1 study specifically addresses JSpA[184]. Most data are extrapolated from studies of JIA (LOE I, SOR B)[185,186,187,188,189,190].

DMARD

Recommendation 6. There are no modifications to the adult recommendations.

Only 2 RCT have assessed SSZ in a pediatric population. In patients with JAS or seronegative enthesopathy and arthropathy, SSZ did not improve primary outcomes, but

improved patient and physician assessments of disease activity[191]. A double-blind, placebo-controlled study of SSZ in juvenile chronic arthritis (including JSpA) demonstrated efficacy and safety in oligo- and polyarticular arthritis[192]. Longterm followup showed prolonged benefit[193]. Chart reviews and open-label studies also support SSZ use[194,195,196,197,198,199,200,201,202,203,204,205].

There are no studies of MTX in JSpA(ERA). One double-blind placebo-controlled RCT of MTX in juvenile rheumatoid arthritis (JRA) showed improvements in joint pain, motion, and APR[206]. Two additional positive RCT exist in JIA[207,208], as do open-label and retrospective studies[209,210,211,212,213].

As with MTX, there are no studies of LEF in JSpA(ERA). An RCT of LEF versus MTX in polyarticular JRA showed that both produced improvement[214]. An open-label study in JRA also demonstrated efficacy and durability[215] (LOE I, SOR A for SSZ; LOE III, SOR C for MTX and LEF).

Antibiotics

Recommendation 7. There are no trials of antibiotics in the treatment of JSpA(ERA). There are no modifications (LOE IV, SOR D).

TNF Inhibitors

Recommendation 8. TNFi are beneficial in JSpA(ERA) and should be prescribed according to predominantly axial or peripheral SpA recommendations. TNFi for JSpA(ERA) treatment include ETN, ADA, and IFX. There is only 1 TNFi RCT in JSpA that demonstrated significant improvements in joint count, ESR, MDGA, and patient global assessment[216]. Open-label studies of IFX[217,218,219] and ETN[217,220] also show TNFi efficacy. Case reports/series of IFX[221,222] and ETN[223] also support TNFi use. A registry showed that ADA was effective in DMARD-resistant ERA[219]. An RCT of ADA in ERA has also shown immediate and sustained efficacy[224]. Several studies have examined the effectiveness of TNFi in JIA (which may include ERA), but an extensive review is considered beyond this paper's scope. LOE I, SOR A for IFX and ADA in JSpA(ERA); LOE II, SOR B for ETN.

TNFi use in JSpA(ERA) has the same barriers to implementation as are present in adults.

Other Biologic Agents

Recommendation 9. To the best of our knowledge, other biologic agents in JSpA(ERA) have not been studied (LOE IV, SOR D).

Surgery

Recommendation 10. There are no specific modifications to the adult SpA recommendations with, to our knowledge, no studies found in JSpA(ERA). The LOE is IV and the SOR is D.

DISCUSSION

The 2014 Update on the CRA/SPARCC Treatment Recommendations for the Management of Spondyloarthritis was developed by a national working group using current literature containing 28 specific treatment recommendations. A treatment algorithm is proposed in Figure 1. Also included are 10 modifications for application to the JSpA(ERA) population. Of note, the majority of these recommendations are based upon evidence from studies of AS and PsA, but we are using these data to inform our recommendations for axial and peripheral SpA in general.

The intent of these recommendations is to inform Canadian rheumatologists, primary care physicians, internists and other healthcare providers, persons with SpA, insurance payers, government agencies, and formularies. It is recognized that each patient is unique and that recommendations cannot be blindly applied to all. Each treating physician should use these recommendations along with their clinical judgment and in partnership with their patients. Ideal SpA management is individualized and specific to each particular patient.

Many questions about SpA management remain unanswered, and barriers to the implementation of these recommendations must be addressed. As the field of SpA management and treatment evolves, updates will be needed.

ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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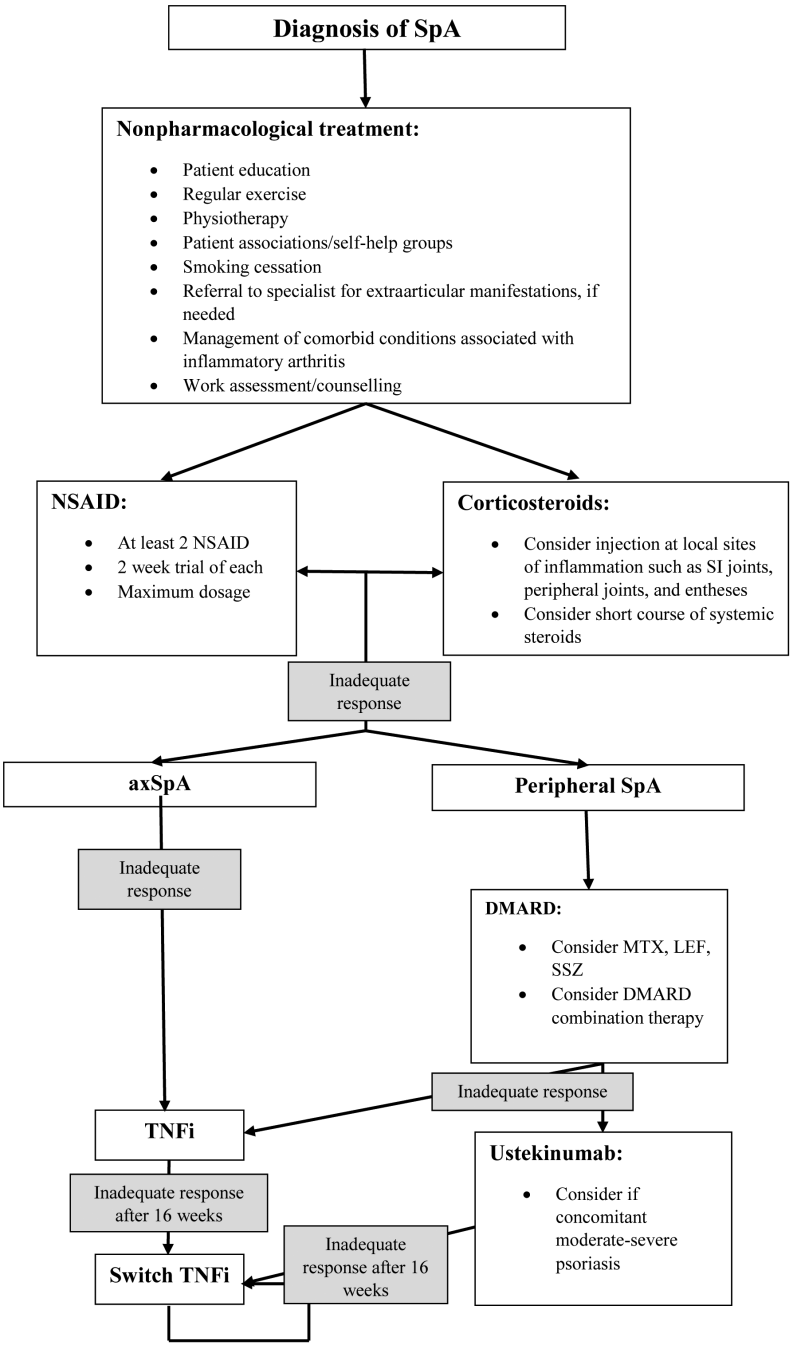

Figure 1. Treatment algorithm for SpA. SpA: spondyloarthritis; NSAID: nonsteroidal antiinflammatory drugs; SI: sacroiliac; axSpA: axial SpA; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; LEF: leflunomide; SSZ: sulfasalazine; TNFi: tumor necrosis factor inhibitors.

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