Online supplement to: 2014 Update of the Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada Treatment Recommendations for the Management of Spondyloarthritis. Part II: Specific Management Recommendations. *The Journal of Rheumatology*. doi:10.3899/jrheum.141001

Online Supplementary Data 1

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

For clarity, these recommendations have been divided into two parts: Part I: Principles of the Management of SpA and Part II: Specific Management Recommendations. Part I addresses optimal SpA management in Canada as well as barriers to implementation of these recommendations and have been presented previously[1]. Part I was largely derived from expert opinion. Part II consists of specific recommendations for SpA treatment and has a larger body of literature support.

Recommendations were based upon the highest quality of evidence available at the time the working group undertook this review. They are intended to promote best practices and improve delivery of healthcare for those with SpA. Recommendations, however, should not be interpreted as rigid or legal standards, or are they intended to replace the clinical judgement of rheumatologists and other trained SpA healthcare providers acting according to the individual needs of the patient and the unique clinical circumstance.

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 the assignment of levels of evidence (LOE) and strength of recommendation (SOR).

RESULTS

The CRA/SPARCC Specific Management Recommendations encompass nonpharmacological treatment, nonsteroidal antiinflammatory drugs (NSAID) and analgesics, corticosteroids, antibiotics, TNF inhibitors (TNFi), other biologic agents, and surgical interventions. These are summarized in Table 2. These management principles may also be applied to juvenile SpA (JSpA) enthesitis-related arthritis (ERA) through a series of modifications summarized in Table 3. The LOE, SOR, and expert opinion score (EO) are listed for each recommendation specifically. Barriers to the implementation of the individual recommendations are also described. These address elements of the Canadian healthcare system that may affect the applicability of the recommendations.

Nonpharmacological

Recommendation 1 advises that nonpharmacological treatment of SpA should include patient education, regular exercise, physical therapy (PT), and involvement in patient associations. PT and exercise interventions in ankylosing spondylitis (AS) have been the subject of systemic literature reviews by both the Assessment of SpondyloArthritis international Society (ASAS) and the Cochrane database[2,3]. The Cochrane review was last updated in 2008 and included 11 trials with 763 participants[2]. The review found individual home based or supervised exercise was superior to no intervention; supervised group PT was better than home exercises and that combined inpatient spa-exercise therapy followed by group PT was better than group PT alone[3]. The ASAS review also included 6 additional papers which confirmed the findings of the Cochrane review[4]. Various exercise programs were found to have moderate-good effect size for Bath Ankylosing Spondylitis Functional Index (BASFI), pain, mobility, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[2]. More recently, a randomized controlled trials (RCT) of inpatient rehabilitation versus usual treatment found that a 3-week program had positive overall effects on disease activity, pain, function, and well-being[4]. Turkish recommendations for PT and rehabilitation in AS have also been recently published[4]. The LOE and SOR for PT in AS are I and A, respectively.

A recent systematic review also examined the effectiveness of exercise programs in AS[6]. This review examined 12 trials with 826 patients with AS[6]. One included trial had an exercise program that met American College of Sports Medicine recommendations for aerobic exercise and had the greatest within-group improvements in aerobic capacity[6]. Small improvements in spinal mobility were demonstrated in all trials. However, the quality of the studies was poor overall[6]. Since that review, 1 clinical trial of home-based exercise therapy showed improved quality of life (QoL) by 3 months; the authors recommended exercise 5 times per week for 30 min per session[7]. The LOE for exercise in AS is II and SOR B.

Recommendation 1 also includes patient education. A pilot study has shown that a 4-day educational program for patients with AS improved disease knowledge and self-rehabilitation at 3 months[8]. An RCT of patients with RA and patients with psoriatic arthritis (PsA) of modular behavioral education versus standard information focused education has shown the former was effective for at least 1 year (decreased pain, improved psychological status, and improved self-management)[9]. Patients polyarthritis, including those with PsA, have been shown to also benefit from group and individual education sessions[10]. Conversely, a single reading of an educational booklet was found to be inadequate in patients with PsA[11]. The LOE and SOR for education in SpA are I, A.

Self-help groups and patient organizations have been included in these recommendations, though there is no specific trial data suggesting enrollment in these organizations improves outcomes (LOE IV, SOR D).

There are currently multiple barriers to implementation of appropriate education, physiotherapy, and to self-help groups in Canada. For the majority of Canadians, these services are not reimbursed by provincial health plans, thus limiting access to those with private insurance. Provincially funded therapies often suffer from lengthy wait lists and geographical limitations. Patients in remote areas may have limited access to self-help groups.

Recommendation 2 states that smoking cessation should be recommended, particularly for patients with axial SpA (axSpA). Several studies have now demonstrated that smoking is associated with worse radiographic outcomes in axSpA. In the GErman SPondyloarthritis Inception Cohort (GESPIC), 210 patients with early axSpA were studied for spinal radiographic progression[12]. Smokers were found to have an increased OR of 2.75 for radiographic progression in comparison to non-smokers[12]. This relationship between smoking and radiographic progression was subsequently found to be dose-dependent[13, 14]. In the same GESPIC cohort, smokers had significant radiographic deterioration in comparison to non-smokers, including new syndesmophyte formation, growth of existing syndesmophytes, and changes in the modified Stoke AS Spinal Score, with the greatest progression found in the heaviest smokers[13]. This association remained after adjusting for other factors which may affect radiographic progression[13]. The French Devenir de Spondylarthropathies Indifférenciées Récentes (DESIR) cohort has also demonstrated the relationship between early axSpA and smoking[15]. In this cohort of 647 patients, smoking was associated with greater axial inflammation and structural damage on magnetic resonance imaging (MRI) and greater damage on radiographs[15]. The affect of smoking on radiographic progression is not limited to early axSpA. Even in patients with longstanding disease ($\geq$ 20 yrs duration), smoking was associated with radiographic severity[16]. Worse radiographic outcomes have also been seen in patients with AS in a smaller study of definite AS[17]. The LOE and SOR for smoking cessation for radiographic progression in SpA is II, B.

Smoking cessation should also be recommended because of its affect on patient outcomes and functional status. In the DESIR cohort of early axSpA, patients who smoked had earlier onset of inflammatory back pain (IBP), higher reported disease activity, poorer functional status and poorer QoL[15]. In patients with longstanding AS, BASFI scores were higher in current smokers compared to former or non-smokers[18]. Multiple other studies have also demonstrated the association between smoking status and functional outcomes[17,19-22]. As with radiographic progression, there has been some evidence that the relationship between smoking and patient reported outcome measures (PRO) may be dose-dependent[23]. Smoking has similarly been found to have a negative affect on functional outcomes in PsA[24]. There is also mounting evidence that smoking is an important environmental risk factor in delaying the onset of PsA among patients with psoriasis[25-27]. The LOE for smoking's affect on patient outcomes and functional status is II, B.

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

NSAID and Analgesics

These recommendations recommend that NSAID are used as first-line drug treatment for symptomatic patients with axSpA. Recommendation 3 states that 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. This recommendation was made because of mounting evidence that NSAID therapy in axSpA is efficacious and may also improve radiographic outcomes, as detailed below.

Several studies have demonstrated that various NSAID, both traditional and selective cyclooxygenase-2 inhibitor (coxibs), are efficacious in AS, both in the long and short-term. A multicenter double-blind, placebo

controlled, 52-week long study of etoricoxib (at 2 doses) or naproxen showed significantly improved clinical outcomes in the treatment groups[26]. A post-hoc subgroup analysis showed that spinal improvement appeared greater in patients without peripheral joint disease[27]. A 12-week RCT of celecoxib (at 2 doses) versus diclofenac demonstrated that both drugs were comparable in terms of clinical outcomes, with fewer gastrointestinal side effects in the celecoxib group[30]. In a trial evaluating short term efficacy of NSAID in active AS, full dose NSAID allowed 29.5% of participants to achieve an ASAS20 response[31]. Recently, an RCT comparing infliximab plus naproxen to naproxen alone showed that naproxen alone led to clinical remission in one-third of the participants[32]. A metaanalysis of RCT evaluating NSAID in AS showed a medium-large effect size for the domains of pain, physical function,n and patient global assessment of disease activity[33]. Other clinical trials also validate efficacy of celecoxib[34,35], meloxicam[36], naproxen[35], aceclofenac[37,38], indomethacin[37-39], pirazolac[31,39], ketoprophen[34], and temoxicam[38,40]. There is some evidence that NSAID and coxibs might have the greatest treatment effect in a subgroup of patients with AS with elevated acute phase reactants (APR)[41].

There is mounting evidence that continuous NSAID use in AS may modify radiographic outcome. A 2-year RCT of continuous versus on-demand celecoxib demonstrated that those in the continuous use group had less radiographic progression[42]. The difference between groups remained even after adjusting for other potentially confounding factors[42]. A post-hoc analysis showed that the slowing of radiographic progression with continuous celecoxib was restricted to those with elevated APR[43]. The GESPIC cohort also recently examined the effect of NSAID on radiographic progression in their large axSpA cohort[44]. This study did not find any difference in radiographic progression with high NSAID intake in the full cohort but there was a difference in a small subgroup of 18 patients with baseline syndesmophytes and an elevated C-reactive protein (CRP)[44]. There was no effect of NSAID use on radiographic progression in the recent study on radiographic progression from North America[14].

The 2-week time period for trial of NSAID was chosen on the basis of knowledge of the half-life of currently used NSAID in Canada[45]. This ranges from 1.5–20 h[45]. Accordingly, a 2-week trial should allow the patient to achieve maximum therapeutic effect. Clinical trials support this timeframe[28,30]. The 2-week trial period is also endorsed by the 2010 ASAS update[46,47]. The working group strongly felt that it was unnecessary to put patients through long trials, since additional improvement was unlikely. A recent editorial emphasizes the need to personalize NSAID use decisions in patients with axSpA[48].

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 discussion of the full literature review for these recommendations is beyond the scope of this article, but are succinctly addressed in a 2008 review paper[45]. The LOE and SOR for these recommendations 4 and 5 are I and A; for 6 they are I, B.

There are no barriers to the implementation of these recommendations.

Recommendation 7 endorses the use of alternative pain control strategies, such as acetaminophen and opioids, in those patients whose symptoms are inadequately controlled by NSAID. Unfortunately, there is a dearth of clinical trial knowledge addressing alternative methods of analgesia in SpA (LOE IV, D for overall recommendation). A Cochrane Review of combination therapy (including analgesics, opioids, opioid-like drugs, and neuromodulators) found no studies that included patients with AS, PsA, or other SpA[49]. One recent, small double-blind, placebo controlled RCT of tramadol 37.5 mg/acetaminophen 325 mg tablets in addition to the NSAID aceclofenac found superior ASAS20 responses in the treatment group[50]. However, there were no differences noted in overall pain, functional outcomes, metrology, APR, or QoL[50]. The treatment group was also noted to have higher numbers of minor adverse events[49].

There are no barriers to the implementation of this recommendation.

Corticosteroids

Recommendation 8 addresses the utility of local corticosteroid injections at sites of inflammation, including the sacroiliac (SI) joints, peripheral joints, and entheses. Three placebo-controlled trials have been performed assessing the utility of corticosteroid SI joint injections[51,52]. Two showed that the treatment groups had significant improvement in pain with minimal adverse effects[52,53], but 1 study found that SI joint injections were ineffective[54]. Two additional studies have assessed computed tomography (CT)-guided intraarticular corticosteroid injections into SI joints with followup by MRI[55,56]. Both showed improvement in patient outcomes as well as significant decreases in MRI evidence of active inflammation[55,56]. Several case series of fluoroscopically guided corticosteroid injections of the SI joints have also demonstrated effectiveness, rapidity, and safety[51,57,58]. Thus, the LOE for local corticosteroid injection into the SI joints is I, with a SOR A. One study has assessed intraarticular steroid injection in PsA[59]. In this large, prospective cohort study, 41.6% of injected joints had a response at 3 months[59]. A longer

duration of psoriasis and those with concomitant methotrexate (MTX) or TNFi use was associated with response[59]. There were no studies assessing intraarticular corticosteroid injections in other types of SpA, or were there studies of entheseal corticosteroid injection. The LOE and SOR for intraarticular corticosteroid injection in PsA specifically is thus II, B. All other intraarticular or entheseal corticosteroid injections are recommended on the basis of expert opinion (LOE IV, SOR D).

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

Recommendation 9 endorses the use of short courses of systemic corticosteroids for specific manifestations, with the caveat that sustained systemic corticosteroid use is not suggested. A recent double-blind, randomized, placebo-controlled trial of oral steroids in patients with AS with active disease, despite NSAID use, found that high dose prednisolone over 2 weeks was effective[60]. Interestingly, low-dose prednisolone was ineffective, which calls into question a previous clinical practice of using steroid-responsiveness to discriminate mechanincal back pain from SpA[60]. Two additional studies, both with small numbers, have addressed pulse methylprednisolone therapy in AS and have suggested possible utility in improving pain and mobility in those who are unresponsive to NSAID[61,62]. The use of systemic corticosteroids in PsA has been historically discouraged due to concern that skin disease may flare upon their cessation. However, 1 study suggested that low-dose corticosteroids in PsA may be fairly common, and greater than the use of systemic steroids in AS[63]. The LOE and SOR of a brief course of systemic steroids in AS are I, A. In all other SpA, the LOE and SOR are IV, D.

There are no barriers to the implementation of this recommendation.

Disease-modifying Antirheumatic Drugs (DMARD)

Recommendation 10 states that there is no evidence for the efficacy of DMARD, including sulfasalazine (SSZ) and MTX, for the treatment of axSpA. A recent Cochrane Systematic Review of MTX for AS identified a total of three RCT of MTX in axSpA, with 116 participants[64-67]. All trials were deemed to be of poor quality[64]. Though 1 trial showed a statistically significant benefit of MTX versus placebo, the authors concluded that there was "no evidence to support any benefit of MTX in the treatment of AS"[64]. A small open-label trial of MTX 20 mg administered subcutaneously similarly showed no benefit for axial manifestations of active AS[68]. Conversely, another small, open-label trial of relatively low dose MTX in AS did show some benefit of MTX on pain, general well-being, metrology, and APR, as well as a reduction in the use of NSAID[69].

The use of SSZ for the treatment of AS has also been studied and has been the subject of a metaanalysis[70,71]. A Cochrane systematic review included 11 studies with a total of 895 participants[70,72-83]. The review concluded that SSZ did have some benefit in reducing morning stiffness and erythrocyte sedimentation rate (ESR)[70]. However, there was no benefit in terms of reduction of pain or improvement of physical function, spinal mobility, or enthesitis[70]. SSZ also failed to affect patient global assessment of disease activity (PGA) and physician global assessment of disease activity (MDGA)[70]. A more recent systematic literature review of SSZ in AS included 6 studies and performed a metaanalysis of 4[84]. This metaanalysis also showed that SSZ had no significant effect on pain scores when compared to placebo[84].

The utility of SSZ in axSpA has been indirectly assessed through comparison with the efficacy of TNFi. SSZ has been compared head-to-head with the TNFi etanercept (ETN) in the ASCEND and ESTHER trials[85,86]. Interestingly, the ASCEND trial did show that the SSZ group experienced some improvements in axial symptoms including total and nocturnal back pain, as well as a53% improvement in ASAS20[85]. A post-hoc analysis of ASCEND also showed ASDAS improvements in the SSZ group[87]. In both of these studies, ETN had significantly greater improvements than did SSZ[85,87]. The ESTHER trial demonstrated a decrease in active inflammation on MRI assessment of patients with axSpA who took SSZ, but again this effect was quite limited in comparison to ETN[86]. A post-hoc analysis also showed that a very small percentage of patients in the SSZ arm were able to achieve a drug-free remission, though once again, significantly less than the ETN group[88]. Unfortunately, the lack of a placebo arms in these studies makes it difficult to derive decisive conclusions regarding the effectiveness of SSZ in axSpA.

Two studies have assessed the effectiveness of leflunomide (LEF) in active AS[89,90]. In a double blind, placebo-controlled RCT, LEF failed to result in significant improvements in ASAS20[89]. An open label trial of LEF in AS showed no improvement in axial symptoms over 6 months[90].

Other potentially disease-modifying agents, such as bisphosphonates and thalidomide, were not considered to be usual therapy by rheumatologists in Canada, and have therefore not been reviewed.

Based on the above metaanalysis, systematic reviews and studies, the LOE for Recommendation 32 is I and SOR A.

There are no barriers to the implementation of this recommendation.

Recommendation 11 addresses the use of the DMARD MTX, SSZ and LEF in peripheral SpA. Most of the data on peripheral SpA derives from studies in PsA. DMARD usage in PsA was recently subject to an extensive systematic literature review and metaanalysis[91].

This review found 3 RCT of MTX versus placebo in PsA with a total of 93 patients, as well as 7 open or retrospective studies[91-101]. The metaanalysis concluded that MTX was effective for the treatment of peripheral arthritis in PsA[91]. Significant effects were found for improvements in tender joint count (TJC) and swollen joint count (SJC)[92-94], pain[93,94], and ESR[92,94]. Only one study assessed the effect of MTX on radiographic progression in PsA, and demonstrated no effect after 24 months of therapy[94]. Interestingly, a subsequent publication suggest that MTX may not be as effective as a DMARD as previously perceived[102]. In this large, double-blind, placebo-controlled RCT of MTX 15 mg/wk, MTX did not improve TJC, SJC, APR, Health Assessment Questionnaire (HAQ), or pain[102]. An editorial accompanying this publication did highlight some issues with the trial design[103].

The above metaanalysis and literature review also assessed the utility of SSZ in PsA[100]. This review found 7 RCT with a total of 666 patients which evaluated SSZ monotherapy versus placebo or active treatment[72,75,91,104-108]. Also reviewed were an open trial and a case-control study[109, 110]. Overall, SSZ was found to be effective, for the treatment of peripheral arthritis in PsA, but minimally so[91]. Only 1 case-control study examined the effectiveness of SSZ in preventing radiographic progression, and found SSZ was ineffective[110].

The effectiveness of LEF in PsA was also recently assessed by Ash, *et al*, who found one relevant RCT and 2 open trials[91,111-113]. The RCT assessed LEF versus placebo over 24 weeks and found it useful for both peripheral arthritis and psoriasis[111]. The open trials also demonstrated positive results for LEF[112,113]. More recently, a prospective 24-week observational study of 514 participants with active PsA treated with LEF showed significant improvements in TJC and SJC and dactylitis as well as PGA, MDGA, and fatigue[114]. This "real world" study allowed patients to remain on concomitant therapy with other DMARD or biologic agents[114].

Other medications studied for the treatment of PsA in include cyclosporine, gold salts, azathioprine, chloroquine, d-penicillamine, fumaric acid, and colchicine[91]. Since these medications are rarely used by Canadian rheumatologists for the treatment of peripheral SpA, they were not extensively reviewed.

Overall, the LOE and SOR for the use of DMARD such as MTX, SSZ, and LEF in peripheral SpA (specifically in the context of peripheral PsA) are I, A. This recommendation is given as the metric we have chosen to evaluate the LOE and SOR assigns high levels to metaanalysis and RCT regardless of potential flaws in study design. The authors of these recommendations noted that the effect of these DMARD, though positive, is clinically minimal.

Recommendation 12 suggests that combination therapy with DMARD should be considered in peripheral SpA, particularly those with poor prognostic factors, greater disease activity, recent-onset disease and in inadequate responders to monotherapy. Unfortunately, this recommendation has little strong evidence. One retrospective study of patients with PsA who had LEF added after failing therapy with MTX suggested the combination may be useful[115]. A double-blind, placebo controlled RCT has also found significant improvements in synovitis in patients with PsA treated with a combination of MTX and cyclosporine[116]. It is anticipated that the TIght COntrol of Psoriatic Arthritis (TICOPA) trial will shed additional light on the practice of combining DMARD in peripheral PsA[117]. Currently, this recommendation has a LOE of IV and SOR of D.

Recommendations 11 and 12 may suffer from barriers to implementation in circumstances where patients have limited drug coverage.

Antibiotics

Recommendation 13 addresses the use of a trial of antibiotics in cases of proven post-*Chlamydia* chronic reactive arthritis (ReA). A recent systematic review and metaanalysis of RCT of antibiotics for ReA concluded that the effects of antibiotics was uncertain[118]. Four trials with a total of 101 subjects assessed the use of antibiotics on *Chlamydia*-related ReA specifically and showed heterogeneous effects[119-122]. The suggested trial of rifampin plus either doxycycline or azithromycin proposed in these recommendations are based upon the findings in 1 prospective, double-blind, placebo controlled trial[119]. Followup studies to confirm these findings have not yet been performed. In view of the findings of the recent metaanalysis, the LOE and SOR for this recommendation is IV, D.

This recommendation may suffer from a barrier to implementation if patients do not have timely access to a physician for appropriate diagnosis and treatment. Drug costs may be an issue for some patients.

TNF Inhibitors (TNFi)

Recommendation 14 addresses the appropriate administration, monitoring, and preventative measures which should be undertaken when prescribing TNFi in patients with SpA. This recommendation is concordant with the Canadian Rheumatology Association recommendations for the management of RA with biologic drugs, which were derived

from a detailed analysis of recommendations worldwide[123]. Despite the widespread acceptance of these suggestions, they are based largely on expert opinion (LOE IV, SOR D).

There are no barriers to the implementation of this recommendation.

Recommendation 15 states that there is no evidence to support the obligatory use of DMARD before, or concomitant with, TNFi in patients with axSpA. This recommendation is based upon the findings of Recommendation 32: there is no evidence for the efficacy of DMARD, including SSZ and MTX, for the treatment of axSpA. The full details for this are outlined above. Recommendations 32 and 37 are both I, A.

There are no barriers to the implementation of this recommendation.

Recommendation 16 identifies that TNFi are efficacious for the treatment of axSpA and details the clinical characteristics of patients with axSpA and for whom treatment with TNFi is indicated. A recent systematic literature review and metaanalysis used to inform the 2012 update of the ASAS/European League Against Rheumatism (EULAR) treatment recommendations in AS assessed the TNFi literature from 2005–2009[124]. This review found 247 reports on the treatment of AS with biologics, of which 98 had efficacy data and 25 had enough data for efficacy analysis[124]. The review included studies on all four of the currently approved TNFi for AS in Canada: infliximab (IFX), etanercept (ETN), adalimumab (ADA), and golimumab (GOL)[124]. In this large review, treatment effect sizes for TNFi versus placebo ranged from 0.34–1.5 for BASDAI[124]. The number needed to treat for all ASAS outcomes ranged between 2.3–3.0 patients[124]. The report concluded that the overall evidence for treatment of AS with TNFi was very high[124]. The literature review also found that TNFi were similarly effective in nonradiographic axSpA (nr-axSpA) and AS[124].

The review conducted by Baralikos, *et al* included studies available in the literature up to and including 2009[124]. Since then, a number of other studies regarding TNFi use in AS have emerged, and certolizumab has been approved in Canada for the treatment of SpA.

Studies of IFX since 2009 have assessed longterm outcomes, dose reduction, radiographic progression, and PRO. In regards to long-term outcomes, continued efficacy, safety, and clinical response to IFX has been shown after 5, 6, and 8 years duration[125-127]. Studies of radiographic progression in IFX-treated patients have shown that longterm use does not lead to an increase in bone formation in the spine and may halt hip radiographic progression[126,128]. Three studies have found that an initial lower dose of IFX for induction is effective, though a majority of patients may subsequently require dose escalation[129,130]. An initial 3 mg/kg dosing regimen was also shown to have a treatment effect on spinal inflammation on MRI[131]. One study found dose reduction from 5 mg/kg to 3 mg/kg of IFX was effective in well-established AS[132]. Regarding PRO, IFX was shown to reduce AS-associated depression[133]. In an open-label study of IFX and ETN over 2 years, those taking IFX were found to have a more rapid clinical response, though both drugs were equally effective, safe, and well-tolerated[134]. The use of IFX + naproxen versus naproxen alone has also been examined, and showed that twice as many patients in the IFX group were able to achieve clinical remission versus naproxen alone[135]. This trial differed from the phase 3 RCT with biologics which included NSAID non-responsiveness as an entry criterion.

The majority of the studies of ETN in AS since 2009 are derived from the ESTHER trial, randomized, multicentre, open-label trial of ETN versus SSZ[86,88,136,137]. ESTHER demonstrated that significantly greater numbers of ETN-treated patients achieved clinical remission and had a reduction in body-wide inflammation as detected by MRI[86,88,136,137]. The ETN group did demonstrate more fatty lesions on MRI than those treated with SSZ, but that there was no significant difference in erosion or ankylosis scores[86,88,136,137]. Neither ETN nor SSZ treatment allowed a substantial number of patients to achieve drug-free remission[88]. The ESTHER study also showed that ETN was equally effective in both AS and nr-axSpA of similar duration[136]. A 16-week RCT of ETN versus SSZ also showed significantly better ASAS20 response rates in the ETN group, without significantly increased rates of adverse events compared to SSZ[85]. One study specifically studied the effects of ETN on the axial manifestations of PsA, showing improvements in BASDAI, BASFI and APR[138].

For ADA, the studies published since 2009 address effectiveness in nr-axSpA, PRO, longterm outcomes, extra-articular manifestations, those with prior biologic use, and effectiveness in Asian populations. In regards to the treatment of nr-axSpA, a 12-week placebo-controlled RCT of ADA in nr-axSpA showed ADA significantly improved ASDAS, BASDAI, and reduced MRI-assessed spinal and SI joint inflammation[139]. ADA was also shown to be effective for retreatment after drug withdrawal in patients with nr-axSpA who flared[140]. Longterm outcomes were assessed by a 5-year open extension of a 24-week ADA RCT[141]. This study demonstrated maintained efficacy and safety in patients with active AS followed for 5 years, with about half of the patients achieving a state of sustained remission[141]. PRO including health-related QoL, sleep, and work outcomes in patients receiving ADA were also assessed, in each case showing beneficial effects of ADA treatment[142-144]. ADA was found to be effective in improving clinical manifestations in patients with AS regardless of psoriasis history[145]. It was also shown to improve enthesitis and peripheral arthritis manifestations of AS[146]. Rudwaleit, *et al* found that ADA could be safe

and effective in patients with AS and PsA with prior treatment with IFX and ETN[147]. Two studies demonstrated effectiveness and safety of ADA in Asian populations[148,149].

Recent publications of GOL in the treatment of AS have focused on the 104-week outcomes of the GO-RAISE study (Efficacy and Safety of GOL in Patients with AS), with efficacy, PRO, MRI, and biomarker data[150]. GO-RAISE was a double-blind, Phase III study of GOL at doses of 50 mg and 100 mg every 4 weeks versus placebo, with an early escape arm at week 16 for non-responders[150]. At 104 weeks, GOL demonstrated sustained clinical response, with 31.9% in the 50 mg group and 30.7% in the 100 mg dosing achieving ASAS partial remission[151]. Safety at week 104 was good and comparable to that at week 24[151]. GO-RAISE 24 week outcomes demonstrated effectiveness of GOL on reducing sleep disturbance in AS[152] . MRI outcomes were also assessed at week 104, with GOL treatment significantly improving spinal MRI inflammation versus placebo[153]. The improvements in MRI spinal inflammation correlated with improvements in ASDAS and CRP in the GOL-treated groups[153]. GOL was also shown to have small-moderate effect on enthesitis[154]. Effects on serum biomarkers were also demonstrated[155].

A fifth TNFi, certrolizumab pegol (CZP), is currently under investigation for the treatment of axSpA. A Phase II, double blind, placebo controlled RCT has studied CZP treatment for 24 weeks in axSpA[156]. The CZP groups showed rapid improvement in the signs and symptoms of axSpA compared to placebo, with no significant differences between those with AS and nr-axSpA[156]. Adverse events were similar to other biologic agents. Of note, CZP has recently been approved for the treatment of SpA in Canada. In the United States, the Federal Drug Administration approved CPZ for the treatment of active AS in October 2013[157].

Recently, it has become evident that TNFi may affect radiographic progression in AS[14]. In a prospective study of 334 patients, TNFi treatment was associated with a 50% reduction in the odds of radiographic progression[14]. The effect seemed to be particularly apparent in those with early TNFi initiation and longer duration of followup[14].

Integrating the data presented above, the LOE and SOR for the use of TNFi in axSpA are I, A.

Recommendation 16 also states that TNFi should be offered to those with persistent active axSpA. These recommendations define active axial disease as the presence of two of: BASDAI > 4, elevated APR, or the presence of inflammatory lesions in the SIJ and/or spine on MRI. This definition of active disease is based on expert consensus; therefore, this portion of recommendation 16 has a LOE and SOR of IV, D.

The major barrier to the implementation of this recommendation is drug cost. Individual provincial coverage for TNFi varies greatly, and even those privately insured may face a large copayment. In some cases, patients may face lengthy application processes before obtaining access to appropriate treatment.

Recommendation 17 addresses the use of TNFi in patients with predominantly peripheral SpA, and states that TNFi should be offered to those with persistent inflammation despite a trial of NSAID and one DMARD. Of note, there is no requirement for the presence of radiographic erosions to be present before TNFi are offered. Most of the literature surrounding the use of TNFi in peripheral SpA is derived from studies of PsA.

The British Society for Rheumatology (BSR) and British Health Professionals in Rheumatology (BHPR) very recently published guidelines for the treatment of PsA, which included a thorough literature review up to July 2011[158]. The literature review on the treatment of peripheral polyarthritis included seven RCT with 1387 subjects (2 ADA, 2 ETN, 1 GOL, 2 IFX)[158]. Each included RCT showed efficacy of the investigated TNFi in treating both American College of Rheumatology composite outcomes (ACR20, 50, 70) and skin manifestations [Psoriatic Arthritis Response Criteria (PsARC)][158]. Unfortunately, no studies were found that specifically addressed the use of TNFi in psoriatic oligoarthritis[158].

A recent literature review and metaanalysis of drug therapies was also performed in the process of developing PsA treatment recommendations by the EULAR[91]. This literature review encompassed a wide time period from 1962–2010[91]. The metaanalysis of biologic agents included 3 TNFi (IFX, ETN, ADA) as well as other non-TNFi biologics[91]. All of the included TNFi showed efficacy at 12-16 weeks for PsARC, ACR composite outcomes, PASI and HAQ[91]. The metaanalysis also demonstrated that all of the studied TNFi repressed radiographic progression of arthritis compared with placebo[91].

Since the above literature reviews were completed, observational studies of biologics in PsA have assessed the safety and efficacy of TNFi in elderly patients and early disease[159,160]. Imaging studies have shown that treatment with IFX significantly reduced ultrasound (US)-detected synovitis and psoriatic plaque thickness[160]. Treatment of PsA with TNFi was shown to impact hepatic steatosis[162]. A "real world" study of consecutive patients with PsA initiating TNFi showed that age, CRP, and BASFI were predictive of minimal disease activity[163]. An indirect comparison of ETN, IFX and ADA versus placebo showed greater ACR20 response in those treated with ETN[164]. Recently, it was demonstrated that TNFi are more effective than MTX in the inhibition of radiographic joint damage progression in PsA[165].

One placebo controlled RCT also addresses the use of ADA in patients with peripheral SpA without AS or PsA, showing significant improvements in BASDAI and ASDAS in the treatment groups[311].For the use of TNFi in peripheral SpA, the LOE is I and SOR A. Recommendation 17 also advises that TNFi be used in those with persistent inflammation despite a trial of NSAID and one DMARD. This component of the recommendation is based on expert opinion (LOE IV, SOR D).

This recommendation also has substantial barriers to implementation. As with axSpA, access to TNFi varies widely from province to province. Cost remains the largest barrier, with potential large copays for the privately insured and strict access requirements for public reimbursement. Some patients may endure prolonged disease activity while waiting to fulfill public reimbursement criteria.

Recommendation 18 addresses the treatment of refractory enthesitis and dactylitis with TNFi. Two studies have assessed the impact of TNFi on enthesitis in patients with SpA[166,167]. A 12 week, double blind, placebo controlled RCT of ETN for the treatment of refractory heel enthesitis related to SpA found significant clinical improvement in the treatment group[168]. A longitudinal study of a small number of patients with SpA treated with ETN for 6 months also found that 86% of entheseal lesions detected by MRI either improved or completely resolved[166]. In PsA, the effect of TNFi on enthesitis (usually the Achilles insertion) has been assessed as a secondary outcome by a number of RCT[158]. Accordingly, RCT of IFX[169,170], ETN[171], ADA[172], GOL[173,174], and CZP[175] have shown that treatment with TNFi improves enthesitis. Regarding dactylitis, there are no RCT that directly address treatment with TNFi. A recent large longitudinal cohort of patients with PsA found that treatment with TNFi was a significant predictor of improvement in dactylitis at 12 months[176]. As with enthesitis, dactylitis is frequently a secondary outcome in RCT of TNFi for PsA[158]. Again, improvement in dactylitis has been shown for IFX[169,170], ETN[171], ADA[172], GOL[173,174], and CZP[175]. The LOE and SOR for TNFi treatment of enthesitis is I, A; for dactylitis the LOE and SOR are II, B.

The major barrier to implementation of this recommendation is access to costly TNFi, as detailed above.

Recommendation 19 states that many TNFi are available for the treatment of SpA, including IFX, ETN, ADA, GOL and CZP, and that the choice of TNFi is based on mutual understanding between the physician and the patient. This recommendation is supported by the RCT outlined above, which demonstrate similar response rates with each TNFi. There are no head-to-head trials which directly compare TNFi , but comparable study design in the Phase 3 RCT has supported the notion of comparable efficacy amongst the TNFi (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 ASAS and GRAPPA, but are based on expert consensus (LOE IV, SOR D)[32,177].

There are no barriers to the implementation of this recommendation.

Recommendation 21 states that the choice of TNFi should incorporate the presence of extra-articular manifestations, such that ideally the chosen drug will treat all conditions. Several TNFi are licensed for treating common extra-articular manifestations in Canada, including plaque psoriasis (IFX, ETN, ADA), Crohn's disease (IFX, ADA) and ulcerative colitis (IFX, ADA, GOL)[178]. Treatment of uveitis with TNFi is currently off label in Canada, but coexistent uveitis may influence the prescriber's choice of drug. A metaanalysis of 4 placebo controlled trials (2 IFX, 2 ETN) showed that both IFX and ETN significantly reduced uveitis flares compared to placebo[179]. An analysis of data from an open-label study of ADA also found substantial reduction in uveitis flares during treatment[180]. A recent economic analysis of the impact of TNFi on uveitis and IBD in patients with SpA found significantly fewer uveitis flares with ADA versus ETN[181]. Similarly, IBD rates were significantly lower in the IFX and ADA groups versus ETN[181]. It is known that the monoclonal antibody (mAb) formulations of TNFi are more effective for the treatment of IBD. Whether this is the case also for uveitis remains unresolved. The LOE and SOR for this recommendation is I, A.

This recommendation may be affected by issues of access. Use of TNFi for the treatment of uveitis is currently off-label[178]. Cost and drug access remains the largest mitigating factor in TNFi usage, as previously described.

Recommendation 22 addresses the combination of TNFi and MTX in SpA, and states that there is no evidence this combination influences clinical efficacy, but may affect persistence in peripheral SpA. For AS, the addition of MTX to IFX has been shown to not significantly impact clinical outcomes, number of infusions, switching of TNFi, dosing interval or pharmacokinetics[182-186]. In PsA, RCT have demonstrated clinical and radiographic efficacy of several TNFi regardless of concomitant MTX use, including ETN[187], ADA[188,189]. Clinical efficacy, independent of MTX use, has also been shown in RCT of IFX[169] and GOL[173]. Concomitant MTX use with TNFi has been shown to improve persistence in PsA in observational studies and registries[190,191]. Lack of concomitant MTX has also been associated with dose escalation of IFX in a registry of patients with PsA[192].

Conversely, two studies have suggested no benefit of MTX in addition to TNFi in PsA[193,194]. One showed a non-statistically significant trend toward better TNFi survival with concomitant DMARD[193]. Both of these negative studies were non-randomized observational cohorts, raising the possibility that concomitant MTX use may have been confounded by indication[193,194]. The component of recommendation 44 that states that combination of MTX and TNFi does not influence clinical efficacy has a LOE of I and SOR A. The component that states that combination TNFi and MTX may be associated with prolonged drug response in peripheral SpA is II, B.

There are no barriers to the implementation of Recommendation 22.

Recommendation 23 states that non-responders to TNFi may benefit from switching to another TNFi. There is no RCT data to support TNFi switching, but a large amount of data from observational studies and registries support this practice.

In AS, in the large Danish DANBIO registry, 30% switched to a second TNFi, and 10% to a third, with 52% of the switchers achieving a BASDAI50 response over 2 years[195]. Women, those with shorter disease duration, and those with worse PROs were at greater risk of switching[195]. In the large Norwegian NOR-DMARD register, about 15% switched TNFi with BASDAI50 responses achieved by 25% of switchers after the first TNFi and 28% after the second TNFi[196]. A real-life study of patients with AS showed a similar 13% switched to a second TNFi with 93% achieving a significant and sustained response[197]. Another retrospective study found increased switching in those with peripheral arthritis and enthesitis, with 32% switching over 29 months and achieving effective responses[198]. Spadaro, *et al* demonstrated that patients with AS treated with a second TNFi had a partial remission rate of 40.5%, which was significantly lower than the response rate to the first TNFi[199]. A small study directly examined switching from IFX to ETN and found it to be effective[200].

Switching has also been shown to be effective in PsA. In DANBIO, 39% of patients with PsA switched to a second TNFi over 10 years[194]. Response rate and drug survival was lower in switchers, but 47% were able to maintain an ACR20 response over 2 years[194]. As seen in the DANBIO patients with AS, female sex, shorter disease duration, and worse PRO predisposed to switching[194]. In the BSRBR, 74% of switchers had response persistence at 12 months[193]. The NOR-DMARD registry also showed effectiveness of switching TNFi in PsA, though switchers had poorer outcomes than non-switchers[201]. A large real-life study in PsA showed about 20% of those receiving TNFi switched, with the majority of patients responding to second or third TNFi[202]. Two small studies have also shown that switching to ADA from other TNFi is effective in PsA[203,204]. The RAPID-PsA study of CZP showed similar efficacy in both TNFi-naive and those with prior TNFi use[175].

Some studies have also examined the issue of switching TNFi in SpA in general, including patients with both AS and PsA. A retrospective study of both axial and peripheral SpA showed that 80.8% responded to a second TNFi and 82.1% responded to a third[205]. The large, observational, Spanish BIOBADASER study also showed good response to switching, though the probability of retaining the second agent was lower than the first[206]. A large Italian study of patients with SpA has also shown a good response to switching TNFi[207]. Smaller studies of patients with SpA have shown that specifically switching from IFX to ETN is effective and from IFX or ETN to ADA is effective[147,208,209].

Since the evidence for switching TNFi agents is largely derived from observational studies, the LOE and SOR of recommendation 23 are II, B.

This implementation of this recommendation may be limited due to cost of therapy. Some private insurance may not cover multiple rounds of TNFi.

Other Biologic Agents

Recommendation 24 states that rituximab (RTX) may be considered for the treatment of axSpA for patients in whom TNFi are contraindicated. RTX is a mononclonal antibody that selectively depletes CD20+ B cells. A small 24-week Phase II clinical trial in established patients with AS showed that those who were TNFi-naive were able to achieve clinical response, while those who were TNFi failures did not[210]. A followup of this study showed that those who responded to RTX at week 24 maintained a good clinical response at the end of 1 year, with about 50% of responders requiring a second course of RTX[211]. A French registry of 26 SpA patents who received RTX also demonstrated a moderate efficacy in those who were not previously exposed to TNFi versus TNFi failures[212]. A small open-label study of 9 patients with PsA has also postulated that RTX may be effective[213]. Case reports have also been published showing clinical and MRI improvement in patients with SpA treated with RTX[214-216]. The LOE and SOR for the use of RTX in TNFi-naive patients with axSpA are II, B.

Of note, RTX is currently not approved by Health Canada for use in SpA[178]. This is a significant barrier to access for patients with SpA. Cost is also an issue.

Recommendation 25 endorses the use of ustekinumab (UST), a monoclonal antibody against IL-12/23, for the treatment of patients with SpA with concomitant moderate to severe cutaneous psoriasis. The recent large

PSUMMIT-I Phase 3 RCT found significantly improved ACR20 responses in those treated with UST compared to placebo, with good safety[217]. A double-blind, randomised, placebo-controlled, crossover Phase 2 study of patients with PsA and ≥ 3% BSA psoriasis also showed that UST was efficacious for reducing signs and symptoms of PsA as well as reducing skin lesions[218]. The same phase 2 clinical trial data also revealed that UST significantly improved physical function and HRQoL compared to placebo[219]. The LOE and SOR for this recommendation are I, A. UST is has recently been approved for the treatment of PsA by Health Canada[178].

Though UST has been recently approved, it does not appear on the provincial formulary universally. This creates a significant barrier to access for many Canadian patients with PsA. Cost is also a significant obstacle to UST use.

Recommendation 26 indicates that there is currently no evidence for the use of other biologic agents in SpA, including abatacept (ABA), tocilizumab (TCZ), and anakinra (ANA). None of these agents are currently approved for the treatment of SpA in Canada[178].

ABA for the treatment of SpA has been studied in small, open-label studies. In a pilot study in AS, there was no observed response both in patients who were TNFi-naive and those who had failed TNFi[220]. Another open-label study in patients with axSpA who had failed TNFi treatment also showed that ABA had no effect on disease activity or function over 6 months of treatment[221]. Interestingly, a 6 month, randomized, double-blind, placebo controlled study of ABA in PsA suggested that it may be effective at a 10 mg/kg dose, potentially indicating a differential effect in peripheral disease[222]. As more data about non-TNFi biologics continues to emerge, the authors anticipate ongoing rapid change in this area. Currently, the LOE and SOR for this part of recommendation 26 are II, B.

TCZ treatment of patients with AS has recently been addressed by the large, placebo-controlled, RCT BUILDER-1 (TNFi-naive patients) and -2 (TNFi-resistant patients)[223]. BUILDER-1 failed to demonstrate efficacy of TCZ, leading to the early discontinuation of BUILDER-2[223]. Case reports of TCZ in AS, PsA and ReA have also been published, with mixed results[224-228]. The component of recommendation 48 regarding TCZ use in SpA has a LOE of I and SOR A.

ANA use for the treatment of SpA has been assessed largely by small, open-label studies. A 3 month open-label study of 9 patients with AS suggested that ANA improved clinical symptoms as well as MRI findings of enthesitis and osteitis[229]. Three of these patients were subsequently reported to have continued improvements with up to 30 months of treatment[230]. Conversely, in a study of 20 NSAID-refractory patients with AS, ANA only improved symptoms in a small subgroup of patients[231]. In PsA, one open-label study of ANA found symptoms improved in 9 out of 20 patients. The LOE and SOR for ANA use in SpA are II and B, respectively.

There are no barriers to the implementation of this recommendation.

Surgery

Recommendation 27 states that total hip arthroplasty (THA) should be considered in patients with refractory pain or disability, and radiographic evidence of structural damage, independent of age. Hip involvement and THA in AS has been studied largely through registries and case series. Data from the Belgian ASPECT, Spanish REGISPOSER and Ibero-American RESPONDIA registries showed 24-36% of their patients had hip involvement, with 5% requiring THA[232]. A single-centre observational study of 275 patients showed 18% had hip involvement, frequently bilateral, with one-third requiring surgical intervention[233]. Those undergoing hip replacement in this group had good outcomes[233]. Several other observational studies of THA in AS have also shown good clinical and functional outcomes, even when the surgeries are performed at a young mean age[234-245]. The calculated survival rate of the arthroplasties at 10 years has ranged from 80-91%[238,239], and up to 70% at 30 years[239]. Interestingly, data from the Norwegian Arthroplasty Register has suggested that the introduction of TNFi may be reducing or prolonging the need for THA[246]. The LOE and SOR for THA in axSpA are II, B.

Unfortunately, there is a paucity of information regarding the need for and outcomes of THA in peripheral SpA such as PsA. Thus, the LOE and SOR for THA in this population would be IV, D.

Barriers to the implementation of recommendation 27 include long joint replacement waiting lists in parts of Canada and access to specialized surgical centres. In some cases, patients may be referred to tertiary care centres with subspecialized surgeons.

Recommendation 28 endorses the use of spinal surgery, for example, corrective osteotomy and stabilization procedures, in selected patients. It also states that ideally, these procedures should be performed at surgical centres with experience in AS spinal disease.

Studies of spinal surgical interventions in SpA are largely case series. Studies have examined correction of chin-brow deformities[247,248], kyphosis[249,250], cervical osteotomy[249,251,252], thoracolumbar osteotomy[250,253,254], lumbar

osteotomy[255-259] and spinal pseudoarthrosis[260,261]. A detailed review of these surgical procedures is beyond the scope of this paper. Recommendation 28 has a LOE of III and SOR C.

The major barrier to the implementation of this recommendation is limited access to specialized surgical centres comfortable in operative and post-operative management of complicated SpA cases. Waiting lists for surgery may be quite long.

Juvenile Spondyloarthritis (JSpA)

Phenotypically, JSpA differs from adult SpA in many ways, generally with more peripheral and entheseal involvement at presentation[262]. JSpA contains several overlapping subtypes, including juvenile ankylosing spondylitis (JAS), juvenile PsA, reactive arthritis, enteropathic arthritis and undifferentiated disease called ERA[262]. Currently, ERA is the most common form of SpA seen amongst children with juvenile idiopathic arthritis (JIA)[262] and the recommendations will address this population specifically. Due to shared familial and genetic predispositions, JSpA(ERA) may be thought of as on a continuum of disease with adult SpA[262]. Indeed, many adult rheumatologists in Canada will manage JSpA(ERA) patients 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) (Table 3).

Nonpharmacological

Recommendation 1 endorses participation in regular physical activity for patients with JSpA(ERA). This recommendation states that children and adolescents with JIA have reduced aerobic fitness, but that participation in exercise does not exacerbate disease. JIA patients have been found to have reduced aerobic and anaerobic exercise when compared with age and sex matched controls[263,264], though one study suggested that this may not be the case in those presenting with oligoarthritis[263]. A Cochrane review of RCT of aerobic exercise in JIA favoured exercise therapy, but the findings were not statistically significant[265]. Importantly, participation in exercise therapy did not exacerbate arthritis[265]. Individual single-blind RCT of exercise interventions in JIA have shown improved outcomes including physical function and QoL[266,267]. Interestingly, a less intensive exercise program (qigong) was as effective as aerobic training and had superior adherence[267]. Of note, JIA includes ERA patients, but there are no studies specifically assessing the effectiveness of exercise in JSpA(ERA) patients. The LOE and SOR for are I and B, respectively.

There are no barriers to the implementation of this recommendation.

The second recommended modification for JSpA(ERA) addresses the fact that peripheral arthritis and enthesitis involving the foot and ankle are common. The use of comfortable, cushioning and supportive foot orthotics is advised. One randomized trial in JIA patients has demonstrated that custom foot orthotics improve pain, speed of ambulation and disability in comparison to off-the-shelf inserts or athletic shoes[268]. Again, this trial may have included ERA patients but did not specifically address JSpA(ERA) (LOE I, SOR B).

Implementation of this recommendation may be limited due to the cost of supportive footwear and custom orthotics. These may not be covered by the patient's or parents' insurance plan.

NSAID and Analgesics

As peripheral arthritis is more common in JSpA(ERA), recommendation 3 recommends that patients should be treated with a longer trial of NSAID of 1–2 months duration. Unfortunately, there are no studies that examine NSAID use in JSpA(ERA). This recommendation is based on expert opinion, LOE IV and SOR D.

There are no barriers to the implementation of this recommendation.

Recommendation 4 states that sacroiliiits in JSpA(ERA) can be managed with NSAID according to the adult axSpA recommendations. Again, there are no trials in JSpA(ERA) to support this recommendation (LOE IV, D).

There are no barriers to the implementation of this recommendation.

Corticosteroids

There are no specific modifications to the adult corticosteroid recommendations. Only one study, published in German, specifically addresses a "JSpA" population[269]. In the English abstract, the authors describe efficacy and safety of CT-guided sacroiliac joint injection with corticosteroids[269]. Intraarticular steroids have also been described as efficacious at multiple sites in JIA[270,271], including the TMJ[272,273], subtalar joint[274], and knee[275]. As the majority of the data is extrapolated from trials in JIA in general, this recommendation has a LOE of I and SOR B.

DMARD

For JSpA(ERA), there are no recommended modifications to the adult recommendations.

SSZ has been studied in only two RCT in a pediatric arthritis population. In patients with JAS or seronegative enthesopathy and arthropathy (SEA) SSZ did not improve primary outcome measures but did improve patient and physician global assessment of disease activity[276]. A double-blind, placebo controlled study of SSZ in juvenile chronic arthritis (including a subset with JSpA) demonstrated efficacy and safety in children with oligo- and polyarticular arthritis[277]. Longterm followup of these patients over a median of 9 years showed prolonged benefit[278]. One retrospective chart review included 21 patients with "JSpA" also showed SSZ was efficacious[279]. A number of open-label studies have also shown SSZ to be effective in JIA[280-290].

There are no studies of MTX in JSpA(ERA). One randomized, double-blind placebo-controlled trial of MTX in juvenile rheumatoid arthritis (JRA) showed significant improvements in joint pain, limitation of motion and APR[291]. Two additional RCT exist in JIA, which included patients with extended oligoarthritis, polyarthritis and systemic disease, and demonstrate improvements in joint counts, patient/physician global assessment and ESR[292,293]. Several open-label or retrospective studies have also shown MTX to be efficacious for JIA[294-298].

As with MTX, there are no studies of LEF in JSpA(ERA). A RCT of LEF versus MTX in polyarticular JRA has shown that both produced high rates of clinical improvement, though the rate was slightly higher in the MTX group[299]. An open-label study of LEF in JRA also efficacy and durability[300].

The LOE and SOR for SSZ are I, A; for MTX and LEF the LOR and SOR are III, C.

Antibiotics

Literature review revealed no trials of antibiotics in the treatment of JSpA(ERA). Thus, there are no specific modifications for this recommendation (LOE IV, SOR D).

TNF Inhibitors

Recommendation 8 states that TNFi are beneficial in JSpA(ERA) and should be prescribed in accordance to the predominantly axial or peripheral SpA recommendations. It also states that the current TNFi available for treatment of JSpA(ERA) are limited to ETN, ADA and IFX. There are few studies of TNFi in "JSpA" specifically, with only one RCT[301]. The RCT of 5 mg/kg dosing of IFX in "JSpA" revealed significant improvements in joint count, ESR, MDGA, and PGA[301]. A 52-week extension phase also demonstrated these improvements in those originally randomized to placebo[302]. Other open-label studies of IFX[303-305], and ETN[303,306] also show that these TNFi are efficacious. Several case reports and case series of IFX[307,308] and ETN[309] also support the use of TNFi. A Dutch biologics registry has also shown effectiveness of ADA in cases of ERA unresponsive to DMARD[305]. A multicentre, randomized, double-blind trial of ADA in ERA has recently shown effectiveness in reducing signs and symptoms at week 12 and sustained efficacy to week 52[310]. Several studies examining the effectiveness of TNFi in JIA (which may have included patients with ERA) have been performed, but an extensive review of these is considered to be beyond the scope of this paper. The LOE and SOR for IFX and ADA in JSpA(ERA) are I, A, whereas ETN has a LOE and SOR of II, B.

Use of TNFi in JSpA(ERA) suffers from the same barriers to implementation as are present in the adult population.

Other Biologic Agents

Recommendation 9 addresses the use of other biologic agents in JSpA(ERA) and states that these drugs have not been studied. A literature search found no trials of RTX, TCZ, ABA, ANA or UST in JSpA(ERA). This has a LOE of IV and SOR D.

Surgery

There are no specific modifications to the adult SpA recommendations for a pediatric population. A literature review revealed no studies of surgical interventions in JSpA(ERA). The LOE and SOR are IV and D, respectively.

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 3. Also included are 10 modifications for application to the JSpA(ERA) population.

Of note, the majority of these recommendations are made based upon evidence from studies of AS and PsA, but we are using this data to inform our recommendations for axial and peripheral SpA in general. 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.

Data Supplement continued in Online Supplementary Data 2…