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Juvenile Spondyloarthritis Treatment Recommendations

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Abstract

No specific recommendations for the treatment of juvenile spondyloarthritis have been established. Important differences exist in how spondyloarthritis begins and progresses in children and adults, supporting the need for pediatric-specific recommendations. Recently published recommendations for the treatment of juvenile arthritis consider children with sacroiliitis in a separate group, and allow for more accelerated institution of a TNF inhibitor depending on disease activity and prognostic factors that derive primarily from studies of other forms of juvenile arthritis. There is a need to develop measures of disease activity and prognosis specific for juvenile spondyloarthritis that reflect spinal disease, as well as other major clinical features such as enthesitis, before significant progress can be made in this area.

Juvenile Spondyloarthritis

Spondyloarthritis in children, or juvenile spondyloarthritis (JSpA), occurs in various forms, including juvenile ankylosing spondylitis (JAS), psoriatic arthritis (PsA), reactive arthritis, and arthritis associated with inflammatory bowel disease. JSpA often presents as an undifferentiated disease that has been classified using the International League of Associations for Rheumatology (ILAR) criteria as enthesitis-related arthritis (ERA), a subgroup of juvenile idiopathic arthritis (JIA). Compared to adults, children are less likely to have symptoms of spinal involvement at disease onset, whereas peripheral arthritis and enthesitis are more prominent. Compared to other forms of JIA, hip and tarsal joint arthritis (tarsitis) are much more likely to occur with JSpA. Despite differences in presentation, juvenile and adult onset SpA share a strong familial predisposition, with well-known genetic overlaps and are likely to represent a continuum in which age, development-related factors, and genetics play a role in determining the precise phenotype and outcome of the disease.

What Is Known About Treatment of Juvenile Spondyloarthritis?

The concept of a disease continuum suggests that medications beneficial in adults with SpA will also be efficacious in juvenile-onset disease. The optimal treatment of children with SpA, however, may differ in important ways due to varying manifestations and evolution of disease. For this reason, specific recommendations for the treatment of JSpA are needed and

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should, when possible, be based on sound clinical evidence. Existing data will be summarized briefly.

NSAIDs

There are no published studies on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in JSpA, although this class of medications is commonly used to relieve symptoms. In adults, NSAIDs have been shown to improve symptoms, reduce inflammatory lesions on MRI, and may slow spinal radiographic progression with continuous use, although the effect is small^{1, 2}.

Sulfasalazine

There has been one randomized controlled trial (RCT) and several open-label trials (OLT) of sulfasalazine (SSZ) in JSpA³⁻⁷. In the RCT, patients with JAS or seronegative enthesopathy and arthropathy (SEA syndrome; similar to ERA) showed improvement, but only in the patient and physician global assessment of disease activity and not in primary outcome measures. The open-label studies of patients with JAS, reactive arthritis, and HLA-B27-positive pauciarticular juvenile rheumatoid arthritis (JRA) showed clinical improvement and some remission. In a separate RCT of patients with juvenile chronic arthritis (JCA) in which 15% of patients had JSpA (ERA or PsA), there was an overall improvement with joint count, patient/physician global assessment, and inflammatory markers⁸. Most studies in adults with SpA suggest a marginal effect of SSZ for peripheral arthritis, and no effect on axial symptoms⁹⁻¹⁴. A recent head-to-head comparison of SSZ and etanercept revealed a surprising effect of SSZ on both axial and peripheral symptoms¹⁵. There was, however, no placebo group, and etanercept was still superior in all parameters measured.

Methotrexate

There have been no studies of methotrexate (MTX) in JSpA. In other subtypes of JIA (extended oligo- and polyarticular, or systemic JIA), RCTs of MTX have shown significant improvement in joint count, patient/physician global assessment, and erythrocyte sedimentation rate (ESR)¹⁶⁻¹⁸.

TNF Inhibitors

Anti-TNF- α agents have been studied to a limited extent in JSpA. There has been one RCT of infliximab (5mg/kg/dose) in JSpA, which demonstrated a significant improvement in arthritis, enthesitis, inflammatory markers, pain, and physical function¹⁹. Improvement in these outcome variables was also seen during the 52-week open extension phase in patients originally receiving placebo²⁰. Similarly, in open-label trials in JSpA (JAS and ERA) infliximab²¹⁻²³ and etanercept²²⁻²⁵ demonstrated improvements in all clinical outcomes. Currently, there is an ongoing RCT examining adalimumab in the treatment of ERA. However, it should also be noted that while TNF inhibitors have striking effects on inflammation and disease activity, there is no clear evidence from adult studies that they halt or even slow the progression of axial radiographic changes²⁶⁻²⁸.

In summary, there is little evidence that either SSZ or MTX are beneficial in JSpA. The lack of controlled trials may be a contributing factor, but where SSZ and MTX have been studied in adults with SpA, they do not appear to be beneficial in axial disease and have limited efficacy in peripheral arthritis. Similarly, there may be some benefit of SSZ in the peripheral arthritis of JSpA. In contrast, although only limited studies have been performed to date, there is evidence that TNF inhibitors are beneficial in JSpA, consistent with results from multiple adult SpA trials. Moreover, both peripheral arthritis and enthesitis, two important therapeutic targets in JSpA, appear to be responsive to TNF inhibition.

ACR Recommendations for the Treatment of Juvenile Arthritis

Recently, an international panel of expert pediatric rheumatologists using the RAND/UCLA Appropriateness Method established recommendations for the treatment of JIA that were endorsed by the American College of Rheumatology (ACR)²⁹. The approach was to establish “treatment groups” rather than, for example, using categories established by the JIA classification system. The treatment groups included children with (1) <4 joints involved (cumulative total), (2) >5 joints involved, (3) the presence of active sacroiliac arthritis, (4) systemic arthritis with active systemic features (without active arthritis), and (5) systemic arthritis with active arthritis (without active systemic features). If one considers JSpA in the context of these treatment groups, most patients would be represented in groups 1, 2, or 3 since systemic features are rarely present. Most children with JSpA who have active axial involvement would be in group 3, whereas patients with JSpA who have only peripheral disease would be in groups 1 or 2, provided they have arthritis and not just enthesitis.

Features of poor prognosis and disease activity were also taken into account. Focusing on the active sacroiliitis group, the indicator of poor prognosis is radiographic damage in any joint, defined as erosions or joint space narrowing. “Low” disease activity requires normal back flexion, normal ESR or C-reactive protein (CRP), a physician global of <4/10, and a patient/parent global of <2/10. “High” disease activity requires at least two of three features; an ESR or CRP greater than twice the upper limit of normal, a physician global of >7/10, and a patient/parent global of >4/10. Those who have one or more features greater than low activity, but fewer than 2 features of high activity would be considered to have “moderate” disease activity.

Applying the JIA treatment recommendations to children with active sacroiliitis, a TNF inhibitor is recommended if there is high disease activity and the poor prognostic feature, provided there has been an adequate trial of NSAIDs (1-2 months). In the absence of the poor prognostic feature, patients with high disease activity who have had 3 months of MTX or SSZ would proceed to a TNF inhibitor. A TNF inhibitor is also recommended for patients with moderate disease activity who have had 3 months of SSZ or patients with low disease activity with the poor prognostic feature, provided they have had at least 6 months of SSZ treatment. A TNF inhibitor would also be recommended for JSpA patients who do not have active sacroiliitis but do have active peripheral arthritis (group 1 or 2), but only after 3 to 6 months of treatment with MTX in addition to 1 to 2 months of prior NSAID treatment and often glucocorticoid joint injections.

What We Don't Know about Treatment of Juvenile Spondyloarthritis

The ACR JIA treatment recommendations provide an important resource for pediatric rheumatologists and should benefit many children with juvenile arthritis. However, there are significant limitations in their applicability to JSpA. For example, they do not address enthesitis, a major component of JSpA pathology and an important therapeutic target that can produce prominent symptoms even in the absence of peripheral or axial arthritis. In addition, the feature for poor prognosis in active sacroiliitis is radiographic damage of *any* joint, defined as erosions or joint space narrowing. This measure is of limited utility when applied to the sacroiliac joint since radiographic evidence of sacroiliitis in SpA may lag behind symptoms for years³⁰. Furthermore, the presenting radiologic feature of sacroiliitis, unlike many other joints, can be joint space widening rather than narrowing, or simply sclerotic changes³¹. The recommendations suggest there must be clinical and imaging evidence of active sacroiliitis, which was not defined. For the last decade there has been a major effort to define early axial involvement in SpA. This has led to the development of

classification criteria for “axial SpA”, where active sacroiliitis is defined as evidence of bone marrow edema or osteitis on at least two consecutive slices of MRI³²⁻³⁴.

Disease activity measures for the active sacroiliitis treatment group, as well as the peripheral arthritis treatment groups where other children with JSpA will reside, rely on ESR/CRP levels and physician and patient/parent global assessments. Inflammatory markers in SpA are frequently normal or minimally elevated and often do not reflect clinically active disease. Other clinical parameters such as back or buttock pain should be considered. While normal back flexion is listed as a low disease activity parameter, it is not clear what data support this, and there is evidence from adult clinical trials that spinal flexion measurements are not sensitive to change³⁵⁻³⁸.

The exclusion of enthesitis as a clinical parameter means that many JSpA patients with sacroiliac or peripheral joint involvement, who do not meet the criteria for poor prognosis or high disease activity yet have severe enthesitis, would not receive a TNF inhibitor until they have had 3 to 6 months of MTX/SSZ in addition to 1 to 2 months of previous treatment with NSAIDs and/or glucocorticoid joint injections. This seems to be an excessive delay, given the evidence that TNF blockers have been shown to be highly effective in the enthesitis and peripheral arthritis of JSpA, whereas there is minimal evidence that MTX and/or SSZ are effective. Indeed, it's not clear from the literature that there is any justification for using MTX for sacroiliitis or other aspects of axial disease.

The ACR JIA treatment recommendations were established as a reference rather than as strict guidelines, and were not intended to substitute for individualized patient assessment and clinical decision-making²⁹. The authors further emphasized that the recommendations should not be used to deny children access to biologics that significantly ameliorate symptoms and have the potential to modify disease. These caveats deserve further emphasis, particularly in the context of JSpA, for the reasons outlined here.

Priorities for Establishing Recommendations for the Treatment of Juvenile Spondyloarthritis

Applying the ACR JIA treatment recommendations to JSpA exposes many gaps in our understanding of this form of childhood arthritis, and provides an opportunity to consider important priorities. Prognostic features and measures of disease activity that are derived largely from the polyarticular, oligoarticular and/or systemic JIA literature are not optimal for JSpA, and additional disease manifestations common to SpA such as axial arthritis, enthesitis, and dactylitis need to be considered. Currently, there is no standardized measure of enthesitis, making it difficult to study clinical response to medications when this is a major feature of disease. Establishing optimal treatment recommendations for undifferentiated JSpA requires better recognition of early axial disease, assessment of prognostic factors such as HLA-B27 and eventually other new susceptibility genes, and measures of disease activity that are sensitive to change.

For differentiated forms of JSpA such as AS (JAS), treatment recommendations established by the Assessment of SpondyloArthritis International Society (ASAS) apply to children as well as adults, provided they meet the modified New York criteria³⁹. For axial SpA, ASAS has established treatment recommendations for adults that could be adapted for children⁴⁰. The 2010 update recommends that patients with active disease move rapidly from NSAID failure (2 NSAIDs over 4 weeks is sufficient) to a TNF inhibitor. For peripheral arthritis, local corticosteroids may be appropriate, and a therapeutic trial of a DMARD such as SSZ is recommended, but there is no requirement to fail MTX. The main problem with applying these recommendations to children is that to be classified with axial SpA requires 3 months

of back pain. This would exclude, or at least delay, treatment of a number of individuals due to differences in disease presentation in children⁴¹.

One approach to the treatment of JSpA would utilize recommendations established for adults when they are appropriate. For undifferentiated JSpA with heterogeneous clinical features, we favor an approach similar to that used for JIA that considers major disease manifestations as therapeutic targets. It may be necessary to develop an expert opinion-consensus based approach while clinical measures that will be essential for clinical trials are being developed and validated.

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