American College of Rheumatology 2011 Recommendations for the Treatment of

JUVENILE IDIOPATHIC ARTHRITIS

Initiation and Safety Monitoring of Therapeutic Agents for the Treatment of Arthritis and Systemic Features

CLINICIAN'S GUIDE

The objective of this guide is to provide a summary of the ACR 2011 Recommendations for the Treatment of juvenile idiopathic arthritis, which have been reviewed and endorsed by the Arthritis Foundation. This guide is not intended to be used as a stand-alone document and should be used in conjunction with the full manuscript published in the April 2011 issue of Arthritis Care and Research.

Purpose and methodology

The treatment of juvenile idiopathic arthritis has benefitted from several recent major advances; however, to date, no validated guidelines offer recommendations for the treatment of JIA. To develop recommendations for the safest and most effective treatment of JIA, the established RAND/UCLA Appropriateness Method was applied to derive recommendations that are as evidenced-based as possible with the understanding that the published literature often does not provide evidence at the level of detail required to guide decisions in everyday clinical practice. The RAND/UCLA process aims to determine which medical interventions are "appropriate," which is defined as when the health benefits exceed the health risks by a sufficiently wide margin that the intervention is worthwhile. Details of the development of the recommendations can be found in the full manuscript.

Scope

These recommendations cover the initiation and safety monitoring of therapeutic agents in the treatment of JIA, including non-steroidal anti-inflammatory drugs, intra-articular glucocorticoid injections, non-biologic disease modifying anti-rheumatic drugs, biologic DMARDs, and systemic glucocorticoids for the treatment of the systemic features of systemic arthritis. Of note, these recommendations divide JIA into 'treatment groups' instead of the JIA categories set forth by International League of Associations for Rheumatology.

These recommendations were developed with international input and are intended to inform and benefit health care providers caring for children with JIA throughout the world. Many recommendations fall outside the present bounds of regulatory agency approved labeling, but reflect common and widely accepted practices in the field.

Therapies that were approved after the original literature review are not included in these recommendations.

Rating the strength of evidence

The levels of evidence associated with the recommendations, as determined using the University of Oxford Centre for Evidence Based Medicine method, are provided in the full manuscript. The levels include:

- **Level A** = randomized clinical trials
- **Level B** = non-randomized controlled studies (e.g., cohort and case-control studies) or extrapolations from randomized clinical trials
- **Level C** = uncontrolled studies (case series), extrapolations from non-randomized controlled studies, or marked extrapolations from randomized clinical trials
- **Level D** = expert opinion without supporting published evidence

INTENDED USE

Guidelines and recommendations developed and/or endorsed by the American College of Rheumatology are intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient. The ACR considers adherence to these guidelines and recommendations to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances. Guidelines and recommendations are intended to promote beneficial or desirable outcomes but cannot guarantee any specific outcome. Guidelines and recommendations developed or endorsed by the ACR are subject to periodic revision as warranted by the evolution of medical knowledge, technology, and practice.

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Initiation of specific therapeutic agents

Four key clinical parameters are defined for each recommendation: JIA treatment group, current treatment, disease activity, and features of poor prognosis. The five JIA treatment groups include:

- *History of arthritis of four or fewer joints*. This group includes patients with the ILAR categories of persistent oligoarthritis, as well as patients with psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis who have developed active arthritis in only four or fewer joints total throughout the history of their disease course.
- *History of arthritis of five or more joints*. This group includes patients with the ILAR categories of extended oligoarthritis, RF negative polyarthritis, RF positive polyarthritis, as well as patients with psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis who have developed active arthritis in five or more joints total throughout the history of their disease. Patients in this group need not currently have five or more active joints.
- *Active sacroiliac arthritis*. This group includes all patients with clinical AND imaging evidence of active sacroiliac arthritis. May include patients from any of the ILAR JIA categories.
- *Systemic arthritis with active systemic features (and without active arthritis)*. This group includes all patients who fulfill the ILAR criteria for systemic arthritis AND who have active fever of systemic JIA with or without other systemic features, but without active arthritis.
- *Systemic arthritis with active arthritis (and without active systemic features)*. This category includes all patients who fulfill the ILAR criteria for systemic arthritis AND who have active arthritis, but without active systemic features.

Disease activity levels and features of poor prognosis are specific to each JIA treatment group and are listed in Tables 1 through 5.

Table 1. Features of poor prognosis and disease activity for a history of arthritis of 4 or fewer joints

Features of Poor Prognosis *(must satisfy 1)*		
Arthritis of the hip or cervical spine		
Arthritis of the ankle or wrist AND marked or prolonged inflammatory marker elevation		
Radiographic damage (erosions or joint space narrowing by radiograph)		
Disease Activity Levels		
Low Disease Activity *(must satisfy all)*	**Moderate Disease Activity** *(does not satisfy criteria for low or high activity)*	**High Disease Activity** *(must satisfy at least 3)*
1 or fewer active joints	1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity	2 or more active joints
Erythrocyte sedimentation rate or C-reactive protein level normal		Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
Physician global assessment of overall disease activity < 3 of 10		Physician global assessment of overall disease activity ≥ 7 of 10
Patient/parent global assessment of overall well-being < 2 of 10		Patient/parent global assessment of overall well-being ≥ 4 of 10

Table 2. **Features of poor prognosis and disease activity for a history of arthritis of 5 or more joints**

Features of Poor Prognosis *(must satisfy 1)*		
Arthritis of the hip or cervical spine		
Positive rheumatoid factor OR anti-cyclic citrullinated peptide antibodies		
Radiographic damage (erosions or joint space narrowing by radiograph)		
Disease Activity Levels		
Low Disease Activity *(must satisfy all)*	**Moderate Disease Activity** *(does not satisfy criteria for low or high activity)*	**High Disease Activity** *(must satisfy at least 3)*
4 or fewer active joints	1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity	8 or more active joints
Erythrocyte sedimentation rate or C-reactive protein level normal		Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
Physician global assessment of overall disease activity < 4 of 10		Physician global assessment of overall disease activity ≥ 7 of 10
Patient/parent global assessment of overall well-being < 2 of 10		Patient/parent global assessment of overall well-being ≥ 5 of 10

Table 3. **Feature of poor prognosis and disease activity for active sacroiliac arthritis**

Feature of Poor Prognosis		
Radiographic damage of any joint (erosions or joint space narrowing by radiograph)		
Disease Activity Levels		
Low Disease Activity *(must satisfy all)*	**Moderate Disease Activity** *(does not satisfy criteria for low or high activity)*	**High Disease Activity** *(must satisfy at least 2)*
Normal back flexion	1 or more features greater than low disease activity level AND fewer than 2 features of high disease activity	Erythrocyte sedimentation rate or C-reactive protein greater than twice upper limit of normal
Erythrocyte sedimentation rate or C-reactive protein level normal		
Physician global assessment of overall disease activity < 4 of 10		Physician global assessment of overall disease activity ≥ 7 of 10
Patient/parent global assessment of overall well-being < 2 of 10		Patient/parent global assessment of overall well-being ≥ 4 of 10

Table 4. **Feature of poor prognosis and disease activity for for systemic arthritis with active systemic features (and without active arthritis)**

Features of Poor Prognosis
6 month duration of significant active systemic disease, defined by: fever, elevated inflammatory markers, or requirement for treatment with systemic glucocorticoids
Disease Activity Levels *(2 levels)*
Active fever AND physician global assessment of overall disease activity < 7 of 10
Active fever AND systemic features of high disease activity (e.g., significant serositis) that result in physician global assessment of overall disease activity ≥7 of 10

Table 5. **Features of poor prognosis and disease activity for systemic arthritis with active arthritis (and without active systemic features)**

Features of Poor Prognosis *(must satisfy 1)*		
Arthritis of the hip		
Radiographic damage (erosions or joint space narrowing by radiograph)		
Disease Activity Levels		
Low Disease Activity *(must satisfy all)*	**Moderate Disease Activity** *(does not satisfy criteria for low or high activity)*	**High Disease Activity** *(must satisfy at least 3)*
4 or fewer active joints	1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity	8 or more active joints
Erythrocyte sedimentation rate or C-reactive protein level normal		Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
Physician global assessment of overall disease activity < 4 of 10		Physician global assessment of overall disease activity ≥ 7 of 10
Patient/parent global assessment of overall well-being < 2 of 10		Patient/parent global assessment of overall well-being ≥ 5 of 10

Current treatment is depicted directly in the recommendation figures. For all recommendations, it is assumed that patients have received the maximum tolerated typical dose of prior medications, as listed in Supplementary Appendix B. Of note, the dose of methotrexate is assumed to be 15 mg/m^2 (0.6 mg/kg) and administered via the parenteral route. For recommendations in which duration of therapy is not defined, it is assumed that the duration of therapy is sufficiently long to assess the response to therapy.

Figures 1 through 4 depict the recommendations for initiation of therapeutic agents for the treatment of JIA. Therapy is escalated as one moves downward in each figure. If the key clinical parameter criteria listed for escalation of therapy are not met, then the recommendation is to continue current therapy along with adjunct NSAID or glucocorticoid joint injections as needed. Recommendations for reduction of therapy are not addressed.

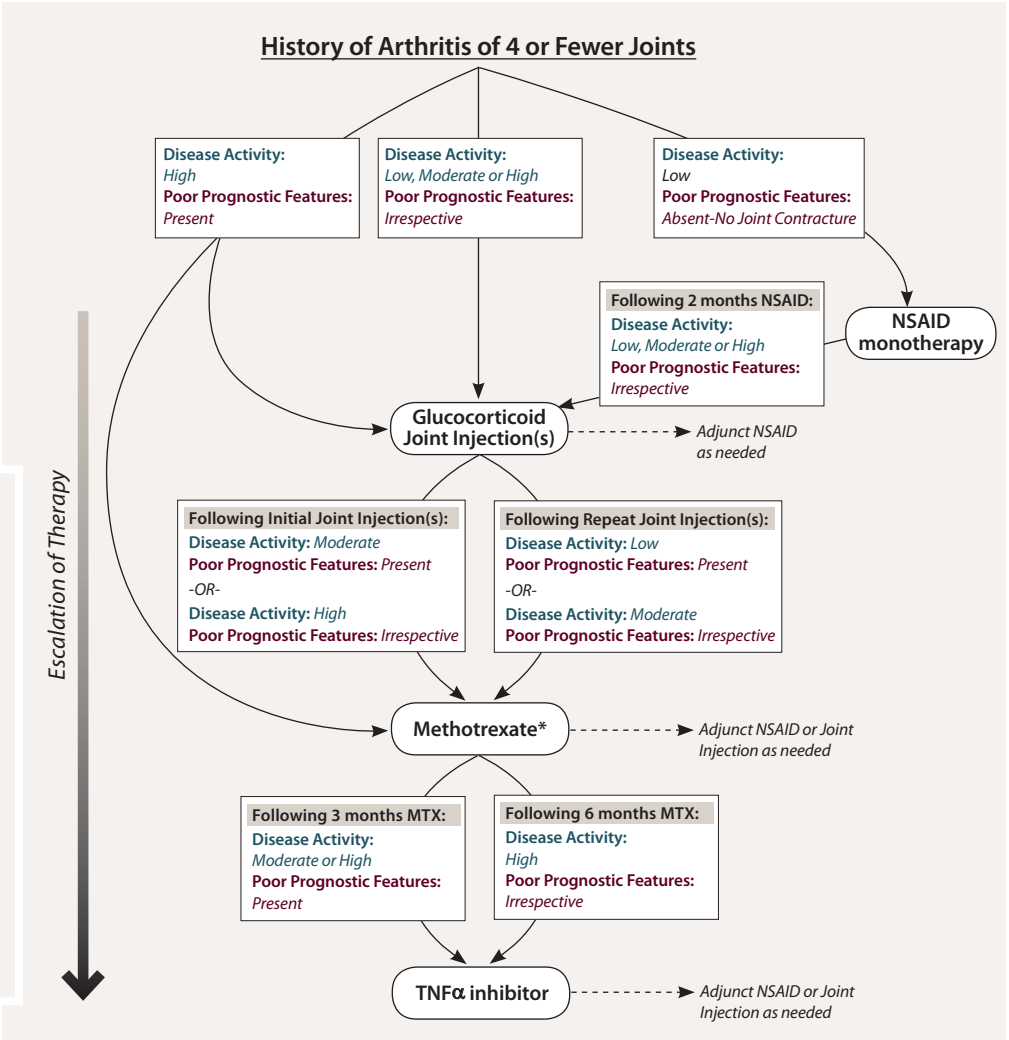

Figure 1. **Treatment recommendations for patients with a history of arthritis of 4 or fewer joints.** These recommendations are intended for patients with juvenile idiopathic arthritis (JIA) who have only developed active arthritis in 4 or fewer joints in total throughout the history of their disease course and are based upon duration of current therapy, disease activity, and features of poor prognosis. If criteria for escalation of therapy are not met, then continue current therapy along with adjunct nonsteroidal antiinflammatory drugs (NSAIDs) or glucocorticoid joint injections, as needed. Recommendations for reduction of therapy are not addressed. See Table 1 for definitions of disease activity and features of poor prognosis. *=sulfasalazine may be an appropriate treatment for patients with the enthesitis-related arthritis category of JIA (see text in full paper for details); MTX=methotrexate; TNFα=tumor necrosis factor α.

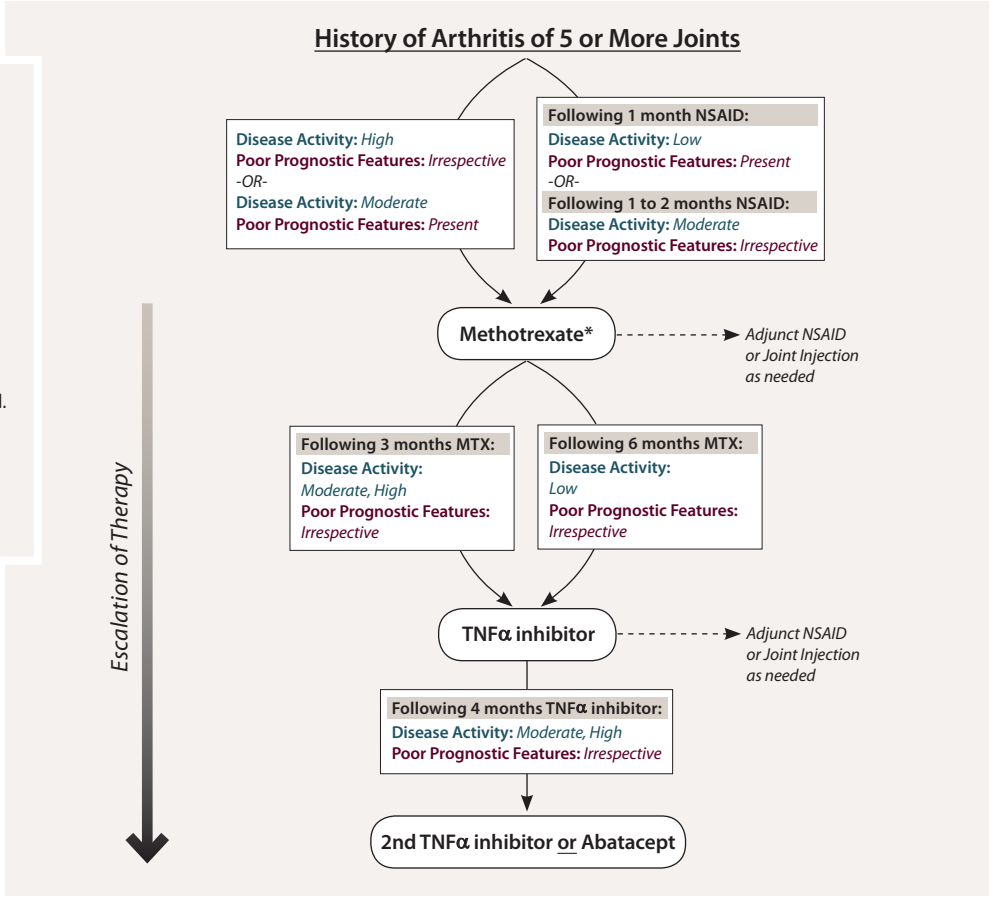

Figure 2. Treatment recommendations for patients with a history of arthritis of 5 or more joints. These recommendations are intended for patients with juvenile idiopathic arthritis who have developed active arthritis in 5 or more joints in total throughout the history of their disease and are based upon duration of current therapy, disease activity, and features of poor prognosis. If criteria for escalation of therapy are not met, then continue current therapy along with adjunct nonsteroidal antiinflammatory drugs (NSAIDs) or glucocorticoid joint injections, as needed. Recommendations for reduction of therapy are not addressed. See Table 2 for definitions of disease activity and features of poor prognosis. *=leflunomide may be an appropriate treatment alternative (see text in full paper for details); MTX=methotrexate; TNFα= umor necrosis factor α.

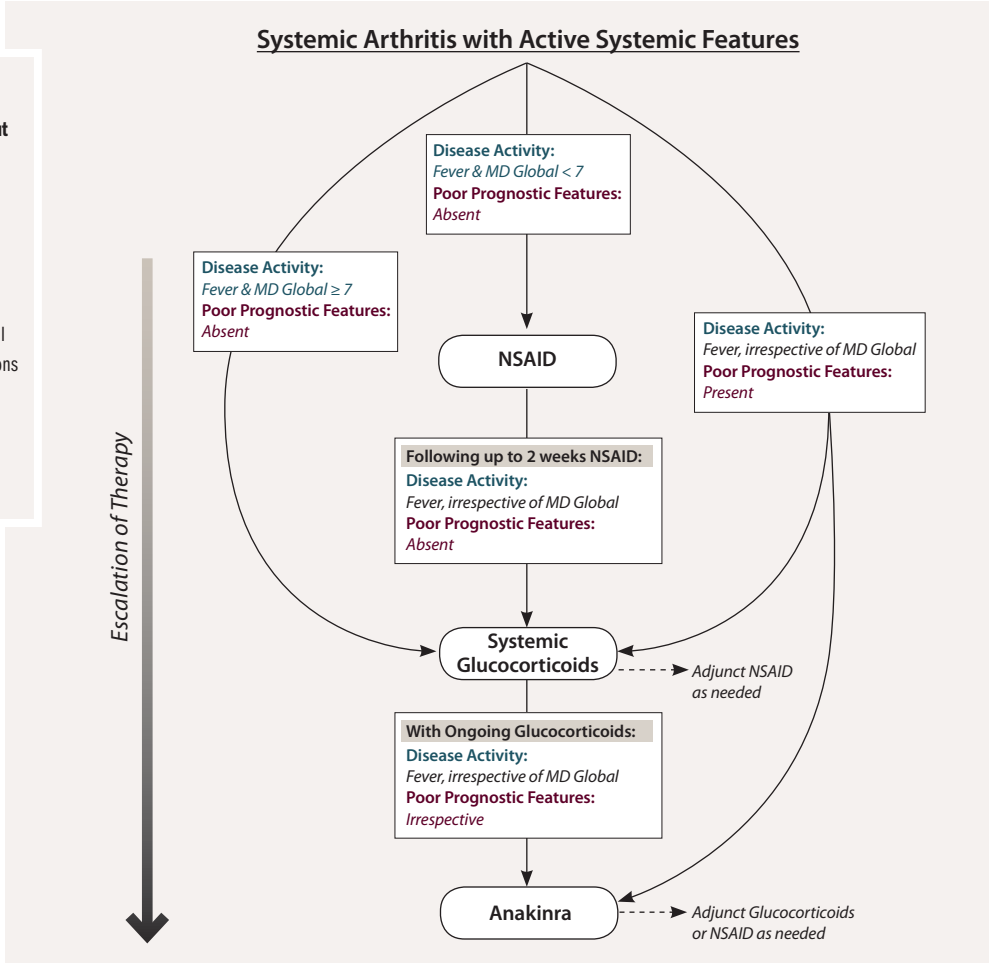

Figure 3. Treatment recommendations for patients with systemic arthritis and active systemic features (and without active arthritis). These recommendations are intended for patients with juvenile idiopathic arthritis who have systemic arthritis with active systemic features and without active arthritis. Recommendations are based upon duration of current therapy, disease activity, and features of poor prognosis. If criteria for escalation of therapy are not met, then continue current therapy along with adjunct nonsteroidal antiinflammatory drugs (NSAIDs), as needed. Recommendations for reduction of therapy are not addressed. See Table 4 for definitions of disease activity and features of poor prognosis. MD Global=physician global assessment of overall disease activity (range 0–10).

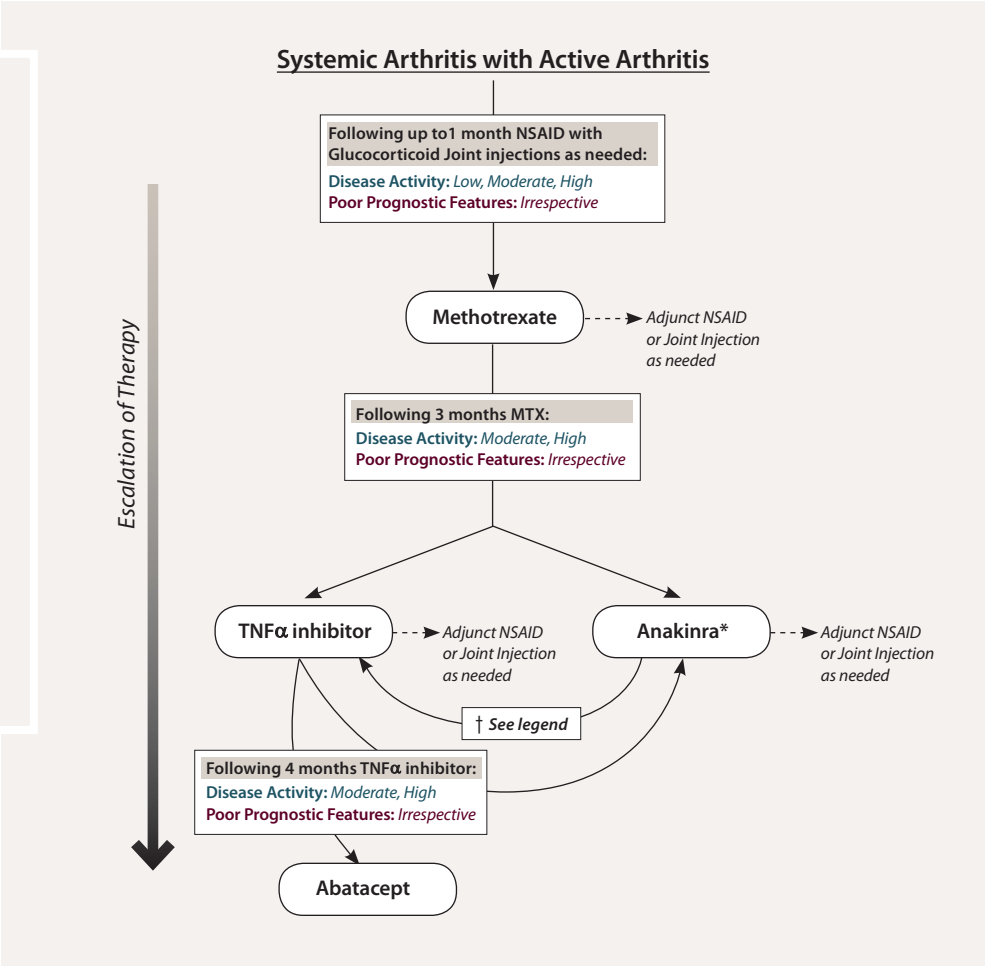

Figure 4. Treatment recommendations for patients with systemic arthritis and active arthritis (and without active systemic features). These recommendations are intended for patients with juvenile idiopathic arthritis who have systemic arthritis with active arthritis and without active systemic features. Recommendations are based upon duration of current therapy, disease activity, and features of poor prognosis. If criteria for escalation of therapy are not met, then continue current therapy along with adjunct nonsteroidal antiinflammatory drugs (NSAIDs), as needed. Recommendations for reduction of therapy are not addressed. See Table 5 for definitions of disease activity and features of poor prognosis. MTX=methotrexate; TFNα=tumor necrosis factor α; *=initiation of anakinra for the treatment of arthritis may be less appropriate later in the disease course compared to nearer the onset of disease; †=switching from anakinra to a TNFα inhibitor may be appropriate for some patients with moderate or high disease activity, irrespective of features of poor prognosis, but there is a possible risk of unmasking latent systemic features when discontinuing anakinra.

The recommendations for active sacroiliac arthritis are summarized below.

Recommendations for patients with active sacroiliac arthritis

Initiation of TNFα Inhibitor is recommended for patients who satisfy the following key clinical parameter criteria:

Prior Treatment	Disease Activity	Features of Poor Prognosis
Adequate trial of NSAIDs	High	Present
Methotrexate for 3 months	High	Irrespective
Methotrexate for 3 months	Moderate	Present
Methotrexate for 6 months	Moderate	Absent
Sulfasalazine for 3 months	Moderate or high	Irrespective
Sulfasalazine for 6 months	Low	Present

Safety monitoring

The recommendations for medication safety monitoring are summarized in Table 6.

Table 6. Summary of recommendations for medication safety monitoring

Non-steroidal anti-inflammatory drugs (NSAIDs)
Complete blood cell count, liver enzymes, serum creatinine · Prior to or soon after initiation of routine use · Repeat approximately twice yearly for chronic daily use · Repeat approximately once yearly for routine use (3-4 days per week)
Methotrexate
Complete blood cell count, liver enzymes, serum creatinine · Prior to initiation · Approximately 1 month after initiation · Approximately 1–2 months after increase in dose · Repeat approximately every 3–4 months if prior results normal and dose stable
Tumor Necrosis Factor α Inhibitors
Complete blood cell count, liver enzymes, serum creatinine · Prior to initiation · Repeat approximately every 3–6 months
Tuberculosis screening · Prior to initiation · Repeat approximately once yearly

Notable Recommendations for Initiation of Biologic Agents

JIA Treatment Group	
History of 4 or fewer active joints	Initiate TNF-α inhibitor if significant arthritis proves refractory to methotrexate
History of 5 or more active joints	Initiate TNF-α inhibitor if low disease activity remains following 6 months of optimal methotrexate
	Initiate abatacept if inadequate response to TNF-α inhibitor
Active sacroiliac arthritis	Lower threshold for initiation of TNF-α inhibitor compared to patients without active sacroiliac arthritis
Active systemic features (fever)	Initiate anakinra as the first steroid-sparing agent

For more information

For electronic copies of the Clinician's Guide, the full guideline, or details about the evidence review and guideline development process, click here or reference the April 2011 issue of *Arthritis Care and Research*.

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