Effective Health Care Program

Muscle, Bone, and Joint Conditions
Juvenile Idiopathic Arthritis

Disease-Modifying Antirheumatic Drugs in Children With Juvenile Idiopathic Arthritis

Focus of the Research for Clinicians

In response to a request from the public regarding the expanding use of disease-modifying antirheumatic drugs (DMARDs) to treat juvenile idiopathic arthritis (JIA), a review was undertaken to examine the effectiveness, benefits, and adverse effects of DMARDs, to compare these drugs with each other and with conventional anti-inflammatory treatments. The systematic review included 56 clinical studies published before 2011, reporting treatment effects in children 18 years of age or younger. The full report, listing all studies, is available at www.effectivehealthcare.ahrq.gov/dmardsjia.cfm. This summary, based on the full report of research evidence, is provided to inform discussions of options with patients and to assist in decisionmaking along with consideration of a patient's values and preferences. Reviews of evidence should not be construed to represent clinical recommendations or guidelines.

Background Information

JIA (see subtypes on Page 2) is the most common rheumatic disease of childhood. The estimated prevalence ranges from 7 to 400 per 100,000 children. JIA can place a severe physical and psychological burden on affected children, with the potential of permanent disability.

DMARDs block the production or activity of the immune cells that cause joint inflammation. Methotrexate, a nonbiologic (synthetic) DMARD, is widely considered part of usual care, along with conventional, nonsteroidal anti-inflammatory drugs and intra-articular corticosteroids. The biologic DMARDs block the action of tumor necrosis factor-alpha (TNF-α) or other immunostimulating cytokines and are anticipated to lead to more disease remissions, but their long-term safety is not fully understood. Anti-TNF-α DMARDs carry United States Food and Drug Administration "boxed warnings" due to their association with lymphoma and serious infections.

The evidence supporting DMARDs for treatment of adult rheumatoid arthritis and other immune disorders is substantial and has been extrapolated to treatment of JIA. However, a synthesis of the clinical evidence from studies of JIA is needed to support decisionmaking that balances the benefits of controlling destructive joint disease against the risks of adverse effects.

Conclusions

Moderate-strength evidence indicates that adding methotrexate to anti-inflammatory drugs for JIA leads to greater improvement in disease activity. The use of a biologic DMARD improves symptoms and decreases the risk of a flare.

How short- and long-term benefits and adverse effects of DMARDs differ across JIA categories is not understood. Few studies of sufficient size make direct comparisons of DMARDs in well-characterized patient populations; thus, it is not clear in which circumstances one DMARD will yield better outcomes than another. How DMARDs affect markers of inflammation and radiographic progression of JIA is not established in the clinical literature. Evidence about the rates, types, and severity of adverse events is too limited to permit conclusions about risks. No single instrument for measuring disease activity or functional status has been identified as clearly superior.

Clinical Bottom Line *(Adverse Effects on Page 2)*

Benefits

General Findings on DMARDs in JIA

- Health status improves with treatment, but statistically significant differences from controls are not consistent. ●○○
- Evidence is insufficient to state how DMARDs affect markers of inflammation and radiographic progression. ○○○
- There are few head-to-head comparisons of DMARDs, either within or between classes. It is not known if any one DMARD or class of DMARDs provides more benefit than any other. ○○○

Nonbiologic DMARDs

- Adding methotrexate to care with anti-inflammatory treatments improves disease activity, as scored by physicians. ●●○
- In the only direct comparisons to date (penicillamine or sulfasalazine vs. hydroxycholoroquine; leflunomide vs. methotrexate), symptoms and health status outcomes were similar, but the studies were not large enough to reveal statistically significant differences. ●○○

Biologic DMARDs

- For children who responded to a biologic DMARD after inadequate response to methotrexate, continued treatment reduced the risk of a flare by 54 percent (*RR = 0.46, valid range at $p < 0.05$ is from 40% to 64% less, NNT†= 3). ●●○
- Etanercept and infliximab provide similar benefits for health status and symptoms. ●○○

†NNT = number needed to treat; *RR = relative risk (risk ratio)

Strength of Evidence Scale

High:	●●●	There are consistent results from good-quality studies. Further research is very unlikely to change the conclusions.
Moderate:	●●○	Findings are supported, but further research could change the conclusions.
Low:	●○○	There are very few studies, or existing studies are flawed.
Insufficient:	○○○	Research is either unavailable or does not permit estimation of a treatment effect.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Clinical Bottom Line *(Continued from Page 1)*

Adverse Effects

Biologic and Nonbiologic DMARDs

- There are few direct comparisons of DMARDS with one another in patients with JIA, and the evidence is insufficient to determine if there are differential rates of adverse events between specific drugs or drug classes. ○○○

The evidence is too limited for quantitative assessments of risks, but these qualitative observations can be made:

- Some patients with JIA developed cancer during treatment with anti–TNF-α antibodies, but the level of risk for all children with JIA is not known. ○○○
- More laboratory abnormalities were associated with methotrexate and more serious adverse events and infections were associated with a combination of infliximab and methotrexate than with other DMARDs of both classes. ○○○

Subtypes of JIA

- Systemic arthritis
- Oligoarthritis
- Rheumatoid-factor positive (RF+) polyarthritis
- Rheumatoid-factor negative (RF-) polyarthritis
- Enthesitis-related arthritis
- Psoriatic arthritis
- Undifferentiated

Evaluation of Assessment Instruments

Current evidence of the validity, reliability, and responsiveness of the clinical outcomes measures used in the composite assessments (such as the American College of Rheumatology Pediatric-30) reveals limitations in the ability of these measures to categorize disease status or response to therapy.

- No one instrument or outcome measure appears superior in measuring disease activity or functional status.
- Reliability and validity are moderate for measures of physical function but poor for psychosocial domains.
- The Child Health Assessment Questionnaire (CHAQ) is the most extensively evaluated instrument to assess health/disease status for patients with JIA. It shows high reproducibility and internal consistency but only moderate correlations with indices of disease activity and quality of life and poor to moderate responsiveness to change.
- CHAQ responsiveness appears to be sensitive to the degree of disability at baseline.
- An outcome measurement instrument that accurately describes all aspects of JIA—including disease activity, functional status, and quality of life—is needed to improve comparative studies of treatments and understanding of the overall impact of JIA.

Gaps in Knowledge

The systematic review identified areas where evidence about the use of DMARDs to treat JIA is limited or absent, including:

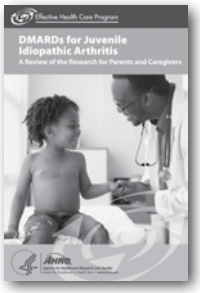
- The comparative effectiveness of DMARDs has rarely been examined in direct, head-to-head studies.
- The effects of DMARDs on measures of inflammation and radiographic progression are not understood, and their impact on JIA-associated conditions, such as uveitis and macrophage activation syndrome, has not been examined.
- The evidence is too limited to understand how patient characteristics, disease subtype, and variability in the disease process affect response to treatment.
- There are few high-quality data about the safety of DMARDs. Standardized definitions, measurement, and reporting of adverse events associated with DMARDs are needed, together with long-term data collection.

What To Discuss With Your Patients and Their Caregivers

- The role of DMARDs for reducing symptoms.
- The natural history of the disease and the potential benefits and adverse effects of DMARDs.
- The importance of communicating symptoms to you and completing any assessment questionnaire you use.
- Patient and caregiver preferences and values regarding treatment.

Resource for Patients

DMARDs for Juvenile Idiopathic Arthritis, A Review of the Research for Parents and Caregivers is a free companion to this clinician research summary. It covers:



- A description of JIA and non-DMARD treatments used to address symptoms.
- The types of DMARDs that are used.
- The limited evidence about the short- and long-term benefits and adverse effects associated with DMARDs used to treat JIA patients.
- Costs related to biologic and nonbiologic DMARDs.

Ordering Information

For electronic copies of *DMARDs for Juvenile Idiopathic Arthritis, A Review of the Research for Parents and Caregivers* (AHRQ Pub. No. 11-EHC039-A), this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

The information in this summary is based on *Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA)*, Comparative Effectiveness Review No. 28, prepared by the Duke University Evidence-based Practice Center under Contract No. HHSA-291-2007-10666-I for the Agency for Healthcare Research and Quality, September, 2011. Available at www.effectivehealthcare.ahrq.gov/dmardsjia.cfm. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

AHRQ Pub. No. 11-EHC039-3
September 2011