Comparative Effectiveness Review
Number 28

Effective Health Care Program

Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA)

Executive Summary

Background

Juvenile idiopathic arthritis (JIA) is the most common rheumatologic disease in childhood, with an overall prevalence of 7 to 400 per 100,000 children. JIA is an important cause of chronic disease in childhood, with prevalence similar to type I diabetes mellitus. Several classification systems have been used over time to categorize the various categories of juvenile arthritis, including juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA), based upon clinical presentation and disease course. In 1995, the International League of Associations for Rheumatology (ILAR) proposed a new classification system, JIA, which consists of seven main categories. These categories are useful in examining potential differences in treatment response and prognosis. The main categories of JIA are:

- Systemic arthritis: Initial presentation includes spiking fever, rash, and arthritis; one-quarter of children who present in this way may have severe destructive disease.
- Oligoarthritis: Affects up to four joints within the first 6 months of illness; may be persistent (i.e., involving no more than four joints) or extended (i.e., involving more than four joints after the first 6 months of illness), and may be associated with uveitis.

Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

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- Rheumatoid-factor positive (RF+) polyarthritis: Affects five or more joints during the first 6 months of disease, and is more likely to result in destructive joint disease. May be associated with uveitis.
- Rheumatoid-factor negative (RF-) polyarthritis: Affects five or more joints during the first 6 months of disease. May be associated with uveitis.
- Enthesitis-related arthritis: May be associated with uveitis.
- Psoriatic arthritis: May be associated with uveitis.
- Undifferentiated: Arthritis lasting more than 6 weeks that does not meet the criteria for any of the above categories, or that meets the criteria for more than one category.

JIA can place a severe physical and psychological burden on affected children and can be a major stressor to their families. As is true for all chronic conditions in childhood, treatment of JIA may be enhanced through the use of a multidisciplinary team to address these issues. There is no cure for JIA, but over the past 25 years new therapies have provided great advances in treatment and symptom control. Previous treatments with nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., ibuprofen) and corticosteroids (systemic or intra-articular) were only partially effective in treating the symptoms of arthritis and reducing long-term complications (e.g., growth delay, erosive joint disease, persistently active disease, mortality). Treatment with the class of agents known as disease-modifying anti-rheumatic drugs (DMARDs) has become an increasingly important component of care because these drugs appear to lead to better disease control, with higher numbers of children achieving remission, and fewer children suffering long-term joint damage. DMARDs interfere with the making or working of immune cells that cause joint inflammation and are typically classified as either biologic drugs, which are created by biologic processes, or non-biologic drugs, which are manufactured chemically. In general, the nonbiologic DMARDs are older. Most biologic DMARDs target specific components of the immune system (e.g., signaling or cell-surface molecules). One of these non-biologic DMARDs, methotrexate, whose exact mechanism is unknown, has been used for so long in the treatment of JIA that it is often considered part of conventional treatment, along with NSAIDs and intra-articular corticosteroids.

Although there is significant optimism that treatment with the newer biologic DMARDs may increasingly lead to long-term disease remission, there are many unanswered questions about the safety of these drugs, especially for long-term use in children. For example, the U.S. Food and Drug Administration (FDA) recently placed a box warning on the entire class of biologic DMARDs targeting tumor necrosis factor (TNF) alpha, including etanercept, infliximab, and adalimumab, due to concerns about potential increased risk of malignancy, in particular lymphoma. There are also important questions about effectiveness, including the comparative effectiveness of DMARDs versus conventional treatment and the comparative effectiveness of the various DMARDs versus one another. Furthermore, it is possible that the effectiveness of these drugs varies by category of JIA. Understanding the circumstances in which a DMARD should be used, and which DMARD(s) should be selected, is challenging because JIA is heterogeneous across the various categories. A clear synthesis of the available evidence is needed, to help clinicians provide care for children with JIA, and to identify the important gaps in the scientific literature.

Juvenile arthritis has a broad impact on a child's physical and mental health. Developing instruments that accurately assess the effect of JIA on health and well-being is critical to enable us to assess the overall impact of the disease and to quantify the efficacy of treatments. The heterogeneity of disease severity, the broad age range of affected individuals, and fluctuations in the natural history of the disease complicate the measurement of disease activity and treatment effects in children with JIA. To provide the most accurate assessment of treatment effects we depend on the performance characteristics (e.g., sensitivity, specificity, responsiveness to change) of the outcomes measures reported in the scientific literature. Multiple instruments have been developed or adapted to assess severity of disease, disability, and quality of life in JIA. Understanding the reliability, validity, and responsiveness of these instruments will facilitate interpretation of clinical trial data.

This comparative effectiveness review summarizes the evidence on the benefits and harms of DMARDs compared to conventional treatment (NSAIDs and/or intra-articular corticosteroids) with or without methotrexate, and of the various DMARDs compared to one another, in children with JIA. In addition, this review summarizes the usefulness of selected tools commonly used to measure clinical outcomes associated with JIA.

Key questions addressed are:

Key Question 1. In children[a] with JIA,[b] does treatment with DMARDs,[c] compared to conventional treatment (i.e., NSAIDs or corticosteroids) with or without methotrexate,[d] improve laboratory measures of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

(a) "Children" are defined as individuals aged 18 years or younger.

(b) "JIA" includes any category of any severity of the following:

- JIA according to the International League of Associations for Rheumatology (ILAR) criteria;
- Juvenile rheumatoid arthritis (JRA) according to the American College of Rheumatology (ACR) definition; or
- Juvenile chronic arthritis (JCA) according to the European League Against Rheumatism (EULAR) criteria.

(c) DMARDs evaluated are: abatacept, adalimumab, anakinra, canakinumab, etanercept, infliximab, intravenous immunoglobulin (IVIG), rilonacept, rituximab, and tocilizumab (biologic DMARDs); and azathioprine, cyclosporine A, penicillamine, hydroxychloroquine, leflunomide, methotrexate, mycophenolate mofetil, sulfasalazine, tacrolimus (FK506), and thalidomide (nonbiologic DMARDs).

(d) Conventional treatments evaluated are: betamethasone, triamcinolone acetonide, triamcinolone hexacetonide, celecoxib, etodolac, ibuprofen, indomethacin, meloxicam, naproxen, oxaprozin, and tolmetin.

Key Question 2. In children with JIA, what are the comparative effects of DMARDs[e] on laboratory markers of inflammation or radiological progression, symptoms (e.g., pain, symptom scores), or health status (e.g., functional ability, mortality)?

(e) This question is identical to Key Question 1, but focuses on comparisons of one DMARD versus another, rather than on comparisons of DMARDs versus conventional treatments.

Key Question 3. In children with JIA, does the rate and type of adverse events[f] differ between the various DMARDs or between DMARDs and conventional treatment with or without methotrexate?

(f) Because of the known risks associated with DMARDs, we focused primarily on serious infections and the development of cancer when assessing adverse events. Other adverse events considered included mortality, hepatitis, bone marrow suppression, nausea or vomiting, and risks to a fetus or pregnant mother.

Key Question 4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories[g] of JIA?

(g) Categories of JIA include:

- Systemic arthritis
- Oligoarthritis
- Rheumatoid-factor positive (RF+) Polyarthritis
- Rheumatoid-factor negative (RF-) polyarthritis
- Enthesitis-related arthritis
- Psoriatic arthritis
- Other (arthritis of unknown cause with symptoms lasting more than 6 weeks).

Key Question 5. What are the validity, reliability, responsiveness, and feasibility of the clinical outcomes measures[h] for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?

(h) The outcomes measures assessed were those most commonly used in clinical trials and practice, as well as newer instruments of particular interest that were selected in consultation with the project's technical expert panel (TEP). The outcome measures assessed were:

- Measures of disease activity:
  - Active joint count (AJC)
  - Physician global assessment of disease activity (PGA)
  - Parent/patient global assessment of well-being (PGW)
- Measure of functional status/disability:
  - Childhood Health Assessment Questionnaire (CHAQ)
- Measures of health-related quality of life:
  - Child Health Questionnaire (CHQ)
  - Pediatric Quality of Life Inventory (PedsQL) 4.0
  - Pediatric Quality of Life Inventory Rheumatology Module (PedsQL-RM)
- Composite measures of response to therapy and developing definitions of disease status:
  - American College of Rheumatology Pediatric Response Criteria (ACR Pediatric 30)
  - Juvenile Arthritis Disease Activity Score (JADAS)
  - A consensus-based definition of remission
  - Flare
  - Minimal disease activity (MDA)

These instruments were assessed for test-retest reliability, inter- and intra-rater reliability, internal reliability, construct validity, responsiveness (standardized response mean and responsiveness index), and feasibility metrics such as time to administer.

Conclusions

Table A provides an aggregated view of the strength of evidence and brief conclusions, based on this review, of the comparative benefits and harms of DMARDs for children with JIA.

Table A. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA

Key question	Strength of evidence	Conclusions
1. In children with JIA, does treatment with DMARDs, compared to conventional treatment:		
a. Improve laboratory measures of inflammation?	Low	Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR—erthrocyte sedimentation rate). However, ESR is inconsistently associated with treatment. This conclusion is based on 14 studies of 1,060 subjects.
b. Improve radiological progression?	Insufficient	Insufficient data are available to evaluate the impact of DMARDs on radiological progression. Only one cohort study of 63 subjects reported data on radiological progression.
c. Improve symptoms?	Moderate	Among children who have responded to a biologic DMARD, randomized discontinuation trials show that continued treatment for from 4 months to 2 years decreases the risk of having a flare (RR 0.46, 95% CI 0.36 to 0.60). This conclusion is based on four studies of 322 subjects. Among the nonbiologic DMARDs, there is some evidence that methotrexate is superior to conventional therapy and oral corticosteroids, based on two randomized trials of 215 subjects.
d. Improve health status?	Low	Changes in health status were reported in 12 studies involving 927 subjects. Health status improved inconsistently with treatment with DMARDs.
2. In children with JIA, what are the comparative effects of DMARDs on:		
a. Laboratory measures of inflammation?	Low	Trials of DMARDs usually report changes in laboratory measures of inflammation (e.g., ESR—erthrocyte sedimentation rate). However, ESR is inconsistently associated with treatment. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects.
b. Radiological progression?	Insufficient	No study addressed radiologic progression.
c. Symptoms?	Low	The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in symptoms between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor-quality RCT of 94 subjects found that etanercept was similar to infliximab.

Table A. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)		
Key question	**Strength of evidence**	**Conclusions**
2. In children with JIA, what are the comparative effects of DMARDs on: (continued)		
d. Health status?	Low	The nonbiologic DMARDs that were compared directly (penicillamine vs. hydroxychloroquine, sulfasalazine vs. hydroxychloroquine, and leflunomide vs. methotrexate) had similar efficacy. Changes in health status between the treatment arms were not measured with significant precision to detect a difference. This is based on 4 RCTs of 448 subjects and 1 cohort study of 72 subjects. One poor quality RCT of 94 subjects found that etanercept was similar to infliximab.
3. In children with JIA, do the rate and type of adverse events differ between:		
a. The various DMARDs?	Insufficient	Three RCTs directly compared two DMARDs; two compared penicillamine to hydroxychloroquine, and one compared leflunomide to methotrexate. The rate and type of adverse events did not differ between treatment groups in these studies. High variability across studies in the ascertainment and reporting of adverse events preclude valid comparisons of the rate and type of adverse events among the various DMARDs. Recently published studies of adverse event reporting databases provide indirect evidence that suggests a possible relationship between cancer and exposure to tumor necrosis factor blockers.
b. DMARDs and conventional treatment with or without methotrexate?	Insufficient	No RCT directly compared a DMARD to conventional treatment. Thirteen trials directly compared a DMARD to placebo. The rate and type of adverse events were generally similar between intervention and placebo groups, with the notable exceptions of infliximab plus methotrexate being associated with more serious adverse events (32% vs. 5% over differing lengths of followup), and methotrexate being associated with higher rates of laboratory abnormalities (35% vs. 13%).

Table A. Summary of the evidence on comparative effectiveness and harms of DMARDs for childhood JIA (continued)		
Key question	**Strength of evidence**	**Conclusions**
4. How do the efficacy, effectiveness, safety, and adverse effects of treatment with DMARDs differ among the various categories of JIA?	Insufficient	Only one study—an RCT of methotrexate versus placebo in which each group could also receive oral corticosteroids, intra-articular corticosteroids, and NSAIDs—evaluated efficacy by JIA category. No difference was found among those with extended oligoarticular JIA (n = 43) and systemic JIA (n = 45). We did not identify any studies that provide reliable information on the comparative safety or rates or types of adverse events among the various categories of JIA.
5. What is the validity, reliability, responsiveness, and feasibility of the clinical outcome measures for childhood JIA that are commonly used in clinical trials or within the clinical practice setting?	Insufficient	Most of the studies examining the psychometric properties of the instrumentsused in JIA were fair-quality cross-sectional or longitudinal nonrandomized controlled trials. No one instrument or outcomes measure appeared superior in measuring disease activity or functional status. The current response criteria of the ACR Pediatric 30, a composite measure that includes articular indices, functional status, laboratory measure, and global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, given that the ACR Pediatric 30 is a relative measure of disease activity, the impact of JIA category on percent improvement is unclear, as certain instruments, such as the CHAQ, appear to have differential responsiveness depending on extent of disease at baseline. The ACR Pediatric 30 is also a relative measure of disease activity and not a measure of current disease state.

Abbreviations: ACR = American College of Rheumatology; CHAQ = Childhood Health Assessment Questionnaire; CI = confidence interval; DMARD(s) = disease-modifying anti-rheumatic drug(s); ESR = erythrocyte sedimentation rate; JIA = juvenile idiopathic arthritis; NSAIDs = non-steroidal anti-inflammatory drugs; RCT = randomized controlled trial; RR = risk ratio.

Remaining Issues

Despite the importance of DMARDs for the treatment of childhood JIA, there is a paucity of comparative evidence for long-term benefits and harms. One particularly important challenge is the development of outcome measure tools that fully describe the impact of the condition and that are both feasible to administer and sensitive to changes in the status of the condition. Some of the measures that are commonly used (e.g., ESR) may not reflect meaningful changes in disease status. Similarly, radiographs to assess joint changes may be difficult to interpret because of the large amount of cartilage. Multidimensional instruments appear to better assess outcomes. Full understanding of the impact of treatment requires understanding not only relative improvement but the overall status of the condition.

Future Research

Although DMARDs have improved health outcomes for children with JIA, few data are available to evaluate the comparative effectiveness of either specific DMARDs or general classes of DMARDs (e.g., non-biologic vs. biologic, or by mechanism of action). Research on the effectiveness of treatments for JIA is challenging because it is a rare condition that includes multiple categories, which could potentially respond differentially to therapy. Furthermore, the health impact of JIA fluctuates over time. Therefore, trials require large sample sizes with long followup periods.

Developing a summary estimate of effectiveness of the DMARDs is challenging because there is:

- *Heterogeneity in the study population*. Changes in the definition of JIA (e.g., JRA, JCA) may have led to the inclusion in studies of individuals who may respond differently to treatments. Similarly, differences by disease category (e.g., polyarticular, pauciarticular, systemic) might lead to different conclusions about the effectiveness of treatment.
- *Variation in comparators*. Over time, the standard of care for JIA has changed. For example, relatively recent studies of biologic DMARDs often allow methotrexate, a DMARD, in the comparator group, while older studies do not include methotrexate in the comparator groups. Some older studies included systemic corticosteroids as a comparator.
- *Variation in outcome measures*. Outcome measures vary across the studies and are sometimes incompletely described. Some studies report the percentage improvement from baseline without providing baseline data or an estimate of variability. Among six randomized discontinuation trials identified for this review, four reported laboratory measures of inflammation, four reported whether a flare occurred, three reported active joint count, and four reported quality of life as measured by CHAQ. Of those that reported the CHAQ score, one reported only the percentage change from baseline without the absolute value or measure of dispersion (e.g., range, standard deviation), and two gave average values without measures of dispersion.

Future trials in this domain should consider:

- *The challenge of the appropriate comparator*. Trials are needed to evaluate the effectiveness of DMARDs compared to conventional therapy as well as against other DMARDs. Defining conventional therapy is challenging because it evolves with advances in the field. Factorial designs involving multiple treatments are a potential solution. Patient-level meta-analysis, pre-planned across different trials, may also help address this issue.
- *The issue of treatment-by-category interaction*. To fully explore comparative effectiveness, larger studies will be needed. In addition, patient-level meta-analysis may help address this challenge.
- *The need for study populations who are representative of typical patients with JIA*. Subjects from the studies included in this review

were identified through specialty clinics, which is appropriate for rare conditions. However, baseline characteristics varied. Studies should be designed to reflect the comparative effectiveness for typical subjects at various points along the disease spectrum (e.g., at presentation, after failing conventional treatment).

- *The variable course of JIA*. Trials that evaluate the efficacy of treatment should be sufficiently long, with frequent assessment of health status, to capture the natural variability of the disease course.
- *Reporting of adverse events*. There is a need for standardized definitions for, and systematic ascertainment and reporting of, adverse events possibly associated with therapeutic interventions in the treatment of JIA.
- *The impact of DMARDs* on the specific health conditions associated with JIA. These conditions include uveitis and macrophage activation syndrome.

Study designs other than randomized controlled trials (RCTs) will be important in understanding the role of DMARDs in JIA. Randomized discontinuation trials have helped to define the risk of flare in patients who respond to a particular DMARD. Large cohort studies will be important for evaluating the risk of adverse events associated with DMARDs. Such studies could also be important for better characterizing long-term outcomes in JIA.

Few high-quality data are available regarding the adverse events associated with DMARDs. Because JIA is a chronic illness, understanding the long-term adverse effects of these drugs is critical. One solution to evaluating risk would be to develop registries for DMARDs when used for childhood JIA. Understanding such risk will also provide information about the sequence in which these drugs should be used for difficult-to-treat JIA, or the impact of using multiple drugs. Implementing more general disease-based registries could not only help assess risk but help evaluate the comparative effectiveness of a wide array of interventions.

Our findings suggest that short-term mortality rates associated with DMARDs are very low—we identified only a single patient among several thousand treated who died shortly after receiving a DMARD. The incidence of malignancies during a short course of DMARD treatment also appears to be very low. However, the available evidence is inadequate to determine whether the rates and types of adverse events differ between the various DMARDs or between DMARDs and conventional treatment. The findings from RCTs do not reveal a clear pattern pertaining to adverse events associated with the treatment of JIA with DMARDs compared to placebo. A review of other study designs revealed marked differences in the rate and type of adverse event by DMARD, but these findings should be interpreted with caution for several reasons, including: variable definitions of adverse events across studies; nonsystematic methods of ascertaining adverse events; nearly universal lack of standard reporting of serious adverse events; a predominance of case reports and uncontrolled series; small sample sizes in most series and RCTs; a limited number of studies for many individual DMARDs; and frequent use of multiple medications and other co-interventions.

Finally, our findings suggest the need for better clinical outcomes measures that are responsive to change across the full spectrum of disease severity. Consistent use of such outcomes measures would facilitate comparative effectiveness research.

The heterogeneity in disease severity and the broad impact of the disease on both physical and psychosocial aspects of children's lives make it difficult to accurately assess children using one instrument or measure. Given the complex nature of JIA, with the potential for both chronic and acute functional limitations and pain, it is difficult to find one tool or instrument that can be responsive to all the facets of disease. Efforts to develop a more standardized composite measure which could incorporate articular indices, severity, and a broader assessment of functional limitations and psychosocial impact would be useful to better differentiate levels of disease activity and overall impact of disease. The current response criteria of the ACR

Pediatric 30 definition of improvement, a composite measure that includes articular indices, functional status, laboratory measure, and global assessments, takes into account the various measures most commonly used. However, the responsiveness of several of these measures, including functional status and parent/patient global assessment, are poor to moderate, and they may not adequately reflect changes in disease state. Furthermore, the ACR Pediatric 30 is a relative measure of disease activity and therefore does not fully describe overall disease status. A relative change in the ACR Pediatric 30 is thus difficult to interpret.

Developing an instrument or composite measure to accurately describe all the aspects of JIA, including disease activity, functional status, and quality of life would improve our understanding of the overall impact of JIA. In addition, focusing on the most responsive outcome measures to assess treatment effects would enhance our ability to detect promising new treatments.

Full Report

This executive summary is part of the following document: Kemper AR, Coeytaux R, Sanders GD, Van Mater H, Williams JW, Gray RN, Irvine RJ, Kendrick A. Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA). Comparative Effectiveness Review No. 28. (Prepared by the Duke Evidence-based Practice Center under Contract No. HHSA 290 2007 10066.) AHRQ Publication No. 11-EHC039-EFRockville, MD: Agency for Healthcare Research and Quality. August 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

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AHRQ Pub. No. 11-EHC039-1
September 2011