Summary of AHRQ’s Comparative Effectiveness Review of Disease-Modifying Antirheumatic Drugs for Children with Juvenile Idiopathic Arthritis

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Target Audiences
This CME activity is designed to meet the educational needs of physicians, pharmacists, nurses, and case managers.

Learning Objectives
Based on the findings from AHRQ’s comparative effectiveness review of disease-modifying antirheumatic drugs for children with juvenile idiopathic arthritis (JIA):

1. Compare the effectiveness of conventional treatments vs. newer synthetic or biologic disease-modifying antirheumatic drugs (DMARDs) for the following outcomes: laboratory measures of inflammation, radiographic progression, symptoms, and health status.
   • Assess the comparative effectiveness of various DMARDs on key clinical, laboratory, and radiographic outcome measures.
   • Summarize the rates and types of adverse events in comparisons among various DMARDs and between conventional treatments and DMARDs.

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4. Print your CME/CE statement immediately following the evaluation

DISCLOSURES

Robert McMahan received compensation from PRIME Education, Inc. for work performed in creating this supplement. Lisa Balfe and Laurence Greene are employees of PRIME Education, Inc., a medical education company that receives grants and funding for educational programs from various pharmaceutical manufacturers. Balfe with the assistance of Greene analyzed the source document, wrote this summary with the assistance of Greene, and revised this summary with the assistance of McMahan.

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DISCLOSURE OF OFF-LABEL USE

The authors report description of uses not approved by the U.S. Food and Drug Administration for the following drugs: anakinra, infliximab, IVIG, penicillamine, hydroxychloroquine, and leflunomide.

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This learning activity was prepared and funded under contract HHSA290201000006G from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS). The activity is intended to inform health professionals about AHRQ’s comparative effectiveness research findings and to identify methods for incorporating the findings into practice. The content in this article is based on the evidence that was available at the time the AHRQ comparative effectiveness review on juvenile idiopathic arthritis was published (September 2011; AHRQ Publication No. 11-EHC039-EF). The full report is available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/108/752/CER28_JuvenileArthritis_20111006.pdf.
Joint damage, and promotion of a high level of functioning are the immediate treatment goals; however, there is no present cure. Inhibition of inflammation, prevention of progression and resolution of disease activity are the ultimate treatment goals; this is typically viewed by patients and families as remission. Remission is considered to be a state in which the patient’s symptoms, radiographic progression, function, and quality of life are normal. The lack of current research for the treatment of JIA motivates AHRQ to contract with researchers to synthesize the available information with the intent of enabling health professionals to make evidence-based practice decisions for their patients. The review also highlights gaps in the research and areas that need to be addressed in the future.

OBJECTIVES: To (a) educate health care practitioners on the findings from AHRQ’s 2011 comparative effectiveness review on DMARDs used to treat children with JIA, (b) apply review findings to make diagnosis and treatment decisions in clinical practice, and (c) recognize limitations and gaps in the current research relating to the comparative benefits and harms of DMARDs for treatment of JIA.

SUMMARY: JIA is a chronic inflammatory disease affecting approximately 300,000 children and adolescents in the United States. Initially manifesting with inflammation, swelling, pain, and stiffness of the joints, the disease does not have an apparent or known cause. JIA is a clinical diagnosis based on several factors including the number of affected joints and the involvement of other tissues (e.g., the skin and lymphoid tissues), and JIA has 7 categories: systemic-onset arthritis, oligoarthritis, rheumatoid-factor positive polyarthritis, rheumatoid-factor negative polyarthritis, enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis. Complete remission and resolution of disease activity are the ultimate treatment goals; however, there is no present cure. Inhibition of inflammation, prevention of joint damage, and promotion of a high level of functioning are the immediate goals of treatment. Even with treatment, patients with JIA continue to experience disease activity, joint destruction, suboptimal function, and impaired quality of life, all of which extend into adulthood. JIA can be severely debilitating and places a heavy physical and psychological burden on children and families affected by the disease.

Methotrexate is a nonbiologic DMARD with an unknown mechanism of action. Methotrexate has been used for so long in the treatment of JIA that it is frequently considered a part of conventional treatment; the evidence shows that methotrexate is superior to conventional treatment with NSAIDs and/or intra-articular corticosteroids. The introduction of newer biologic DMARDs has spawned optimism that treatment will increasingly lead to improved outcomes for JIA, but the evidence is insufficient to support superior outcomes. Methotrexate remains an effective treatment in JIA, with the potential for increased risk of lymphoma caused by the U.S. Food and Drug Administration (FDA) to place boxed warning labels on biologic DMARDs including etanercept, infliximab, and adalimumab. The effectiveness of the DMARDs appears to vary among categories of JIA and the treatment history of individual patients. Except for methotrexate, there is insufficient evidence to support selection of a specific drug or drug class over another in the treatment of JIA.

The AHRQ review examines the scientific literature on DMARDs used in children with JIA in an effort to synthesize what is known about the subject, and the comprehensive review identifies important research gaps in the literature that need to be addressed. Only 8 studies (in 9 publications) were rated “good quality” by the AHRQ investigators.

Conventional JIA treatments—nonsteroidal anti-inflammatory drugs (NSAIDs) and systemic or intra-articular corticosteroids—may only be partially effective in reducing the severity of arthritis symptoms and in minimizing long-term complications. With recent and ongoing advances in the development of DMARDs, experts in rheumatology currently view remission as a potentially achievable goal for many children with JIA. DMARDs act by interfering with the development, activation, or function of immune cells that produce the molecular mediators of joint inflammation and damage in JIA. Nonbiologic DMARDs are manufactured chemically, whereas biologic DMARDs are produced through biologic materials and processes. The nonbiologic DMARD methotrexate has been a cornerstone JIA treatment for many years. Methotrexate is often considered as part of a conventional treatment regimen along with NSAIDs and corticosteroids.

Given the heterogeneity of JIA (Table 1), as well as the numerous treatment options in conventional and DMARD classes (Figure 1), questions naturally arise about the comparative effectiveness of available medications on disease symptoms, radiographic progression, function, and quality of life. Moreover, there are many concerns about the long-term safety risks of JIA medications, especially for use in children. Thus, comprehensive synthesis of published studies in this area would be of great value to clinicians who provide care for children with JIA. 

AHRQ’s Comparative Effectiveness Review of Conventional Therapies and DMARDs for JIA

In September 2011, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of synthetic and biologic DMARDs for JIA treatment in youths.
Summary of AHRQ’s Comparative Effectiveness Review of Disease-Modifying Antirheumatic Drugs for Children with Juvenile Idiopathic Arthritis

TABLE 1  Criteria for Classification of JIA—International League of Associations for Rheumatology (ILAR, 1998)

<table>
<thead>
<tr>
<th>JIA Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arthritis</td>
<td>Arthritis and fever plus 1 or more of the following: (a) rash, (b) lymph node enlargement, (c) hepatomegaly or splenomegaly, (d) serositis</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>Arthritis of 1-4 joints in the first 6 months</td>
</tr>
<tr>
<td>Persistent¹</td>
<td>&lt; 5 joints throughout disease duration</td>
</tr>
<tr>
<td>Extended²</td>
<td>&gt; 4 joints after 6 months</td>
</tr>
<tr>
<td>Rheumatoid-factor negative (RF-) polyarthritis</td>
<td>Arthritis of &gt; 4 joints in the first 6 months of disease, RF-</td>
</tr>
<tr>
<td>Rheumatoid-factor positive (RF+) polyarthritis</td>
<td>Arthritis of &gt; 4 joints in the first 6 months of disease, RF+</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Arthritis and psoriasis OR arthritis and at least 2 of the following: (a) dactylitis, (b) nail abnormalities, (c) family history of psoriasis</td>
</tr>
<tr>
<td>Enthesitis related arthritis</td>
<td>Arthritis and enthesitis OR arthritis or enthesitis with at least 2 of the following: (a) sacroiliac tenderness and/or inflammatory spinal pain, (b) HLA-B27, (c) family history of HLA-B27-associated disease, (d) onset in a male over 6 years of age, (e) acute (symptomatic) anterior uveitis, (f) history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter’s syndrome, or acute anterior uveitis in a first-degree relative</td>
</tr>
<tr>
<td>Other arthritis</td>
<td>Children with JIA who do not fulfill criteria for any category or fulfill criteria for &gt; 1 category</td>
</tr>
</tbody>
</table>

*All JIA categories require age of onset less than 16 years. *Persistent involves no more than 4 joints. *Extended involves more than 4 joints after the first 6 months of illness.


Key Question 1: For laboratory measures, radiographic progression, symptoms, and health status, what are the effects of DMARDs versus conventional treatment with or without methotrexate? For this key question, intermediate outcomes included laboratory measures of inflammation, active joint counts, numbers of joints with limited range of motion, radiographic evidence of disease progression, and global assessment of current health status. Long-term outcomes included clinical remission, joint function, functional ability, pain control, quality of life, growth, development, and mortality. The conventional therapies evaluated in studies included in the AHRQ review are in 2 classes: (a) intra-articular steroids (betamethasone, trimcinolone acetonide, and triamcinolone hexacetonide), and (b) NSAIDs (celecoxib, etodolac, ibuprofen, indomethacin, meloxicam, naproxen, oxaprozin, and tolmetin). The major treatment comparisons analyzed in the included studies are illustrated in Figure 1, and the biologic and nonbiologic DMARDs (e.g., methotrexate) with status of FDA-approval for JIA are listed in Table 2.

Key Question 2: For laboratory measures, radiographic progression, symptoms, and health status, what are the comparative effects of different DMARDs? Analyzing the same outcomes as key question 1, this question focused on head-to-head comparisons of DMARDs.

Key Question 3: Do the rate and type of adverse events differ among DMARDs or between DMARDs and conventional treatments with or without methotrexate? This question primarily addressed treatment-related risks of serious infections and malignancies. In addition, adverse events of interest included nausea, vomiting, hepatitis, bone marrow suppression, mortality, and risks to the fetus or pregnant mother.
Summary of AHRQ’s Comparative Effectiveness Review of Disease-Modifying Antirheumatic Drugs for Children with Juvenile Idiopathic Arthritis

### TABLE 2

<table>
<thead>
<tr>
<th>Biologic DMARDs</th>
<th>Nonbiologic DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Name</strong></td>
<td><strong>Trade Name</strong></td>
</tr>
<tr>
<td>Abatacept</td>
<td>Orencia</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Humira</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Kineret</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Ilaris</td>
</tr>
<tr>
<td>Enanercept</td>
<td>Enbrel</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade</td>
</tr>
<tr>
<td>IVIG</td>
<td>Carmune</td>
</tr>
<tr>
<td>Ritonixib</td>
<td>Rituxan</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Actemra</td>
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</tbody>
</table>


### Literature Search Strategy

The EPC investigators identified published studies for their review through searches of comprehensive databases including MEDLINE and EMBASE, in addition to conference abstracts and reference lists. The review periods covered publications from 1947 through December 2010. The searches included literature from randomized controlled trials (RCTs), nonrandomized comparative studies, case series, and case reports. Study selection criteria were based on relevance with the 5 key clinical questions. Moreover, studies were selected for the review only if they:

1. Were reported in peer-reviewed English-language publications
2. Included individuals with JIA who were 18 years or younger
3. Followed patients for at least 3 months
4. Investigated outcomes for patients treated with at least 1 of the DMARDs (Table 2)

From a total of 4,815 potentially relevant citations identified in the original search, 3,998 were excluded at the abstract screening stage. From the remaining 817 citations, 313 were gray literature documents (e.g., published abstracts, letters to the editor), and 306 other citations failed to meet the inclusion criteria. A total of 198 articles were ultimately included in the review. Several articles were excluded from the review during the abstract screening stage. To evaluate efficacy, the review incorporated prospective trials that included a comparator and that lasted for at least 3 months. No comparator was required to the JIA categories summarized in Table 1, and the 8 studies (9 publications) rated “good quality” are listed in Table 3.

### Key Question 4: How do the efficacy, effectiveness, safety, and adverse events of DMARD treatments differ for children affected by the various categories of JIA?

This question refers to the JIA categories summarized in Table 1, and the 8 studies (9 publications) rated “good quality” are listed in Table 3.

### Key Question 5: How valid, reliable, responsive, and feasible are the various instruments used to assess clinical outcomes in practice settings and clinical trials for patients on JIA therapies?

The assessment instruments that were analyzed to answer this key question are listed in Table 4. The instruments were assessed for test-retest reliability, inter- and intra-rater reliability, internal reliability, construct reliability, responsiveness (standardized response mean and responsiveness index), and feasibility metrics, including time for administration.

### Comparative Effectiveness Review Methods

This section summarizes the methods by which the EPC investigators conducted their comparative effectiveness review of studies on JIA therapies. The topic for this review was nominated publicly and refined by the EPC researchers based on public commentary and input from a panel of technical experts. The process was guided by AHRQ’s commitment to assuring relevance for all key stakeholders. Complete details about the systematic review methods are available in the full technical report.6
### TABLE 3

<table>
<thead>
<tr>
<th>Drug Comparison</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>JIA Category, Sample Size, and Study Design</th>
<th>Key Findings</th>
</tr>
</thead>
</table>
| **Studies of Biologic DMARDs Versus Conventional Treatments with or without Methotrexate**

- **Etanercept vs. placebo** (Lovell et al., 2000)
  - # of patients with disease flare
  - Safety
  - JIA: Polyarticular (n = 62)
  - Pauciarticular (n = 6)
  - Systemic (n = 34)
  - RCT discontinuation with open-label follow-up
  - Flare rates for etanercept
  - No dropouts due to AEs

- **Adalimumab vs. placebo** (Lovell et al., 2008)
  - Disease flare in patients not on MTX
  - ACR Pedi 30/50/70/90/100
  - Safety and adverse events
  - Active polyarticular JRA despite prior treatment with NSAIDs (n=171)
  - RCT discontinuation with open-label follow-up
  - Without MTX, disease flares in 43% of adalimumab patients vs. 71% for placebo
  - More patients reached ACR 50 with adalimumab + MTX vs. placebo + MTX
  - Without MTX, no difference in ACR for adalimumab vs. placebo
  - Patients improved at all levels of ACR
  - 14 patients with serious AEs possibly related to adalimumab vs. 1 patient on placebo

- **Abatacept vs. placebo** (Ruperto et al., 2008)
  - Time to flare
  - ACR pediatric 30/50/70/90
  - Persistent polyarticular JRA despite prior MTX (n = 122)
  - RCT discontinuation with open-label follow-up
  - Flare rate 53% (n = 33 of 62) for placebo vs. 20% (n = 20 of 60) for abatacept
  - Median time to flare 6 months for placebo
  - AE in 55% (n = 34) placebo patients vs. 62% (n = 37) for abatacept

- **Penicillamine vs. hydroxychloroquine** (van Kerckhove et al., 1988; Brewer et al., 1986)
  - Efficacy (AJC, ESR, PGA)
  - Adverse events
  - Pain on movement
  - RCT
  - JRA: Polyarticular (n = 142)
  - Pauciarticular (n = 11)
  - Systemic (n = 9)
  - PGA
  - Median time to flare 6 months for placebo
  - AE in 55% (n = 34) placebo patients vs. 62% (n = 37) for abatacept

- **MTX vs. placebo** (Giannini et al., 1992)
  - Safety
  - Efficacy
  - # swollen joints
  - Pain on motion
  - Tenderness
  - ESR
  - JRA (n = 127)
  - RCT
  - 63% of low-dose MTX (10 mg/m²) patients improved vs. 32% for very low-dose MTX (5 mg/m²) vs. 36% for placebo
  - AEs 13% for low-dose MTX vs. 20% for very low-dose MTX vs. 12% for placebo
  - Only 3 MTX discontinuations (3%) due to mild-to-moderate AEs and none with severe toxicity; no drop-outs due to AEs for placebo

- **Sulfasalazine vs. placebo** (van Rossum et al., 1998)
  - Joint swelling
  - Overall arthritis severity score
  - PGW
  - PGA
  - JCA: Polyarticular (n = 32)
  - Oligoarticular (n = 37)
  - PGA
  - AE rates for sulfasalazine

- **MTX vs. placebo** (Woo et al., 2000)
  - Efficacy
  - ESR
  - PGA
  - PGW
  - Steroid dose
  - Presence of systemic features
  - JIA: extended oligoarticular (n = 43)
  - Systemic (n = 45)
  - RCT with crossover
  - MTX 15-20 mg/m² orally once a week was effective for extended oligoarticular and systemic JIA

- **MTX vs. placebo** (van Kerckhove et al., 1998)
  - Efficacy
  - ESR
  - PGA
  - PGW
  - JRA: Polyarticular (n = 142)
  - Pauciarticular (n = 11)
  - Systemic (n = 9)
  - PGA
  - Median time to flare 6 months for placebo
  - AE in 55% (n = 34) placebo patients vs. 62% (n = 37) for abatacept

*Good quality as defined by the AHRQ criteria: “A ‘good’ study has the least bias and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.”  
*All studies rated “good” quality for the biologic DMARDs compared with conventional treatment with or without methotrexate were randomized discontinuation trials.  
*The AHRQ investigators included Brewer et al. (1986) and van Kerckhove et al. (1998) in 2 categories: “studies comparing nonbiologic DMARDs versus conventional treatments with or without methotrexate” for the primary comparator (placebo) with conventional treatment (NSAIDs, acetaminophen, codeine) and the category for “studies comparing various DMARDs with one another.”  
ACR = American College of Rheumatology; AE = adverse event; AJC = active joint count; CHAQ = Childhood Health Assessment Questionnaire; DMARD = disease-modifying antirheumatic drug; ESR = erythrocyte sedimentation rate; JRA = juvenile rheumatoid arthritis; PGA = physician global assessment of disease activity; PGW = parent/patient global assessment of well-being (PGW); mg = milligram; m² = square meter; MTX = methotrexate; RCT = randomized controlled trial.
IVIG, and tocilizumab) and 8 studies evaluated 5 nonbiologic DMARDs (azathioprine, penicillamine, hydroxychloroquine, methotrexate, and sulfasalazine). The review also included 35 publications that described 34 unique studies of 14,831 patients examining the psychometrics of selected outcome measures or developing definitions of treatment response.

Assessments of Study Quality and Strength of Evidence
To assess the methodological quality of studies included in their review, the EPC investigators used a grading system based on criteria detailed in AHRQ’s Methods Guide for Effectiveness and Comparative Effectiveness Reviews. The quality of individual studies was graded as good, fair, or poor based on the following definitions:

• Good studies are considered valid and relatively unbiased, as evidenced by clear descriptions of their patient populations, settings, interventions, and treatment groups. Moreover, good studies are characterized by valid approaches to allocating patients to groups, low

for reports of adverse events or of the clinical outcome measure tools. Specific inclusion and exclusion criteria were followed for each key question. For RCTs, abstracts were included if there was random allocation to the intervention or placebo group, at least 1 DMARD was evaluated, the study lasted at least 3 months, children in the sample were 18 years or younger, and original data were used. Observational studies incorporated the same inclusion criteria, but specified that cross-sectional studies would only be acceptable for the evaluation of clinical outcome measurement tools not the impact of treatment. For all key questions, the sample population must have JIA according to the ILAR criteria, or JRA according to the ACR definition, or JCA according to the EULAR criteria. Any of the subtypes of JIA/JRA/JCA at any level of severity were acceptable.

Comparisons of DMARDs to conventional treatments with or without methotrexate were identified in 20 publications which included 18 unique studies of 1,532 participants. From these publications, 10 studies evaluated 7 biologic DMARDs (abatacept, adalimumab, anakinra, etanercept, infliximab, and tocilizumab) and 8 studies evaluated 5 nonbiologic DMARDs (azathioprine, penicillamine, hydroxychloroquine, methotrexate, and sulfasalazine). The review also included 35 publications that described 34 unique studies of 14,831 patients examining the psychometrics of selected outcome measures or developing definitions of treatment response.

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dropout rates, and appropriate methods for preventing bias, measuring outcomes, and analyzing results.

- Fair studies are susceptible to bias, although not to a degree that invalidates the results. Fair studies may also be characterized by missing information or methodological weaknesses.
- Poor studies have significant bias that may invalidate their results. Moreover, poor studies tend to have large amounts of missing information and serious errors in design, analysis, or reporting.

In addition to assessing the methodological quality of studies included in the review, the EPC investigators evaluated the strength of study evidence, using a modified version of an instrument developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group.8 This evaluation considers factors regarding the estimation of effects.

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### Measuring Functional Status

The Child Health Assessment Questionnaire (CHAQ), which was adapted from the Stanford Health Assessment Questionnaire (HAQ) for adults, is the most extensively evaluated instrument for measuring functional status and disability in children. The CHAQ is designed to assess disability and discomfort, which are major indications of JIA disease activity. The instrument comprises a disability index (CHAQ-DI; 30 items, 8 domains) and 2 visual analogue scales that assess pain/discomfort and overall well-being, respectively.4 The CHAQ-DI assesses the child’s difficulty in completing various tasks. The form can be completed by the child’s parents. Scores range from 0 to 3, with higher scores reflecting increased disability. The CHAQ is widely used and validated in multiple languages.

### Measuring Health-Related Quality of Life

In children with JIA, health-related quality of life can be measured with the Child Health Questionnaire (CHQ), the Pediatric Quality of Life Inventory (PedsQL) 4.0, and the Pediatric Quality of Life Inventory Rheumatology Module (PedsQL-RM). The CHQ has a 28-item or 50-item form that can be filled out and an 87-item self-administered form for children over 10 years of age. The CHQ addresses many domains including physical functioning, bodily pain or discomfort, general health, range in health, limitations in schoolwork and activities with friends, mental health, behavior, self-esteem, family cohesion, and emotional or time impact on the parent. Scores range from 0 to 100, with higher scores indicating greater well-being.

The PedsQL 4.0 is a self-administered questionnaire that uses brief, generic core questions to measure health-related quality of life in children aged 2 to 18 years. The Generic Core Scales include 23 items that can be facilitated to healthy school and community populations and to children with acute and chronic health conditions.6 The scales are measured on 4 domains including physical, emotional, social, and school functioning. The PedsQL can differentiate between healthy patients and children with acute and chronic conditions, as well as indicate the morbidity and mortality burdens.

The PedsQL-RM contains 22 items that address 5 domains including pain and hurt, daily activities, treatment, worry, and...
communication. The score ranges from 0 to 100, with higher scores relating to a better quality of life. The total score is calculated from the physical score and psychosocial score, the latter of which is calculated from the average of emotional, social, and school functioning scores.

- **Benefits of DMARDs Versus Conventional Therapies**

This section addresses the AHRQ review findings relevant to key question 1 and focuses on the comparative benefits of nonbiologic or biologic DMARDs vs. conventional therapies with or without methotrexate. For each comparison, relatively few studies were identified that met the review inclusion criteria. The small number of studies included in the review, as well as their considerable differences, precluded meta-analyses for most comparisons. Thus, the findings summarized as follows are organized by individual studies and comparisons.

- **Benefits of Nonbiologic DMARDs Versus Conventional Treatments**

Studies included in the AHRQ review compared clinical and functional outcomes for children treated with methotrexate vs. conventional medications.

A poor-quality study (n = 63) reported greater improvements in mean AJC among patients treated with methylprednisolone (-7.1) versus methotrexate (-4) or NSAIDs (-0.8, P = 0.008). However, this study failed to adjust for potential confounders, and patients were not blinded to treatment assignments.

Leflunomide, an immunomodulatory agent not approved by the FDA for JIA, was compared to conventional treatment with methotrexate in only 1 RCT. This RCT (n = 94) was rated as good quality; 86 patients completed 16 weeks of treatment and 70 patients were followed in a 32-week blinded extension period. There was no difference in the reduction in the mean AJC between the leflunomide and methotrexate groups (-8.1 vs. -8.9, respectively; P value reported as “not significant”). Longitudinal improvements in the leflunomide and methotrexate groups for CHAQ scores, PGA, PGW, and ESR. There were trends toward higher rates of ACR Pediatric 30, 50, and 70 responses for patients treated with methotrexate. For example, between weeks 16 and 48, 70% of patients in the leflunomide group achieved an ACR Pediatric 70 response versus 83% in the methotrexate group. However, there was no improvement between week 16 and week 48 for either the leflunomide (P = 0.10) or methotrexate (P = 0.06) groups, and no between-group statistical comparison was made.

- **Benefits of Biologic DMARDs Versus Conventional Treatments**

Adalimumab, a fully human anti-tumor necrosis factor (TNF) alpha monoclonal antibody, was compared with conventional therapy in 1 good-quality randomized discontinuation trial that lasted 48 weeks (n = 171). Outcomes were stratified by whether patients in both groups were also treated with methotrexate. In comparisons of those who did not use methotrexate, the proportion of patients who experienced disease flares was lower in the adalimumab group (43%) versus the conventional treatment group (71%, P = 0.03). Among patients who also used methotrexate, the incidence of disease flares was also lower in the adalimumab group (37% vs. 65%, respectively; P = 0.02). More patients attained the ACR Pediatric 50 score in (a) the adalimumab without methotrexate group than the conventional treatment without methotrexate group (53% vs. 32%, respectively; P = 0.01) and (b) the groups that did receive methotrexate (63% for adalimumab vs. 38% for conventional treatment, P = 0.02). There was no difference in the Pediatric 90 score for adalimumab (30%) versus conventional treatment (18%, P = 0.28).

- **Uveitis**

Uveitis, an extra-articular manifestation of JIA, is rarely found in children with systemic JIA, but more commonly prevalent in children with polyarticular onset. A small placebo-controlled, randomized, double-masked, prospective clinical trial, which was rated as fair quality, found no apparent difference between treatment with etanercept versus placebo in 12 children with uveitis. The study consisted of 2 phases, each lasting 6 months. The first phase was a double-masked randomized study, and the second phase was a single-arm, open-label cohort study. Although this study design was not able to detect a substantial benefit for the use of etanercept in treating JIA-associated uveitis, it is possible that a treatment effect does exist and the study design failed to provide a sufficient sample size with the power to detect such a difference.

Infliximab, another TNF-alpha inhibitor, was compared with placebo in 1 double-blind RCT rated as fair quality despite inconsistent and incomplete reporting of outcomes. The ACR Pediatric 50 response at 14 weeks was 50.0% (29 of 58 patients) in the infliximab group versus 33.9% (20 of 59 patients) in the placebo group (P = 0.078), and there was also no difference in the rate of clinical remission at 52 weeks for infliximab (44.1%) versus placebo (43.1%, no P value reported).

Intravenous immunoglobulin (IVIG) was compared with conventional treatment in 3 studies. A small fair-quality discontinuation trial (n = 19) reported a 3% decrease in the AJC for IVIG-treated patients compared with a 30% increase in the placebo group. The PGA score improved in 3% of the treatment group and worsened in 91% of the placebo group. In a poor-quality, open-label trial (n = 20) comparing IVIG with methylprednisolone for patients with systemic JIA, there were no significant treatment-group differences for changes in ESR over 6 months. In a poor-quality RCT with 31 patients, there were no significant differences in changes in AJC or PGA among patients treated with IVIG versus placebo (0.1% albumin).

Tocilizumab, a humanized antibody directed against the
IL-6 receptor, was compared with conventional treatment for patients with systemic JIA in a fair quality randomized discontinuation trial (n=43) of 56 patients who completed the open-label lead-in phase and achieved an ACR Pediatric 30 response and CRP concentration > 5 mg per dL. There were no P values reported in this study for the outcomes. In the RCT component of this study, the AJC decreased in both the tocilizumab group (from 3.5 to 0) and the conventional treatment group (from 4 to 0). Improvements in CHAQ scores were reported for both groups (-0.5 vs. -0.25, respectively). Both the PGA and PGW also improved, and the ESR decreased for both groups. The percentage of patients achieving ACR Pediatric 70 criteria increased in the tocilizumab group (from “approximately 70% to approximately 80%”) and decreased in the conventional treatment group (from “approximately 80% to approximately 30%”).

Comparative Benefits of Nonbiologic DMARDs or Biologic DMARDs

This section, which addresses the findings relevant to key question 2, focuses on clinical and functional outcomes reported in studies that compared different nonbiologic DMARDs or different biologic DMARDs. Very few studies were identified that directly compared the effects of DMARDs in children with JIA. Moreover, the evidence was generally insufficient to determine whether any specific drug or drug class is associated with better outcomes. No studies included in the AHRQ review compared a nonbiological DMARD with biologic DMARD.

Comparative Benefits of Nonbiologic DMARDs

Penicillamine, an older DMARD with an unknown mechanism that is no longer in routine use as therapy for JIA, and hydroxychloroquine were compared with each other and placebo in 1 good-quality RCT (n=162) described in 2 publications. Both drugs demonstrated equal efficacy for measures of AJC, ESR, and the PGA at 12 months. Another poor-quality, open-label trial (n=72) compared hydroxychloroquine and penicillamine with gold. This study reported no differences in AJC, ESR, and the PGA at 50 weeks. Because penicillamine and gold are no longer used for treating JIA, the clinical relevance of these findings is questionable.

Sulfasalazine was compared with hydroxychloroquine in 1 poor-quality RCT (n=39) that reported no P values for the comparisons. The average number of affected joints decreased by 1.5 in the sulfasalazine group and by 0.6 in the hydroxychloroquine group. The ESR decreased in both the sulfasalazine (52.7 to 36.3) and hydroxychloroquine (41.2 to 28.9) arms. The PGA and PGW scores were similar for both groups.

Comparative Benefits of Biologic DMARDs

The Duke EPC investigators found only 1 published study that directly compared biologic DMARDs for children with JIA. This was a poor-quality, nonrandomized open-label study comparing etanercept with infliximab (n=24). The study methods were flawed by drug switching, lack of blinding to therapy, and withdrawals due to noncompliance and adverse events. Among the 10 children in the etanercept arm, 1 was withdrawn for noncompliance. Among the 14 children receiving infliximab, 4 withdrew due to adverse events and 1 withdrew because of lack of efficacy (failure to attain ACR Pediatric 50 criteria). After 12 months of treatment, there was no difference in the mean decrease in AJCs for etanercept (-9.5, 95% CI=-19 to -3) versus infliximab (-11.5, 95% CI=-17 to -7.5). Treatment-related changes were also similar for etanercept versus infliximab for the following measures: CHAQ score (-0.81 vs. -0.31, P=0.12), PGA (-29.0 vs. -33.0, P=0.65), PGW (-24.5 vs. -27.5, P=0.81), ACR Pediatric 75 (67% for both groups), ACR Pediatric 50 (78% vs. 89%, P=0.53) and ESR (28.5 vs. -25.0, P=0.37).

Comparative Risks of DMARDs and Conventional Therapies

This section addresses key question 3, which focuses on types and rates of adverse events in comparisons between different DMARDs or between DMARDs and conventional treatments. Unfortunately, few head-to-head DMARD trials have been conducted on children with JIA; thus, the evidence is weak for the comparative risks of specific drugs or drug classes. The EPC investigators identified 13 placebo-controlled RCTs that reported adverse events associated with JIA therapies. Rates of adverse events were generally similar across the published RCTs. The review identified 11 incident cases of cancer among several thousand children treated with 1 or more DMARDs. An additional 2 publications identified 66 cases of malignancies diagnosed in children undergoing treatment that included TNF-alpha inhibitors. The EPC investigators recommend interpreting these data with caution, because the adverse events were not systematically collected or reported across the studies. In addition, because some clinical trials excluded patients who did not tolerate an intervention during a drug run-in phase, adverse event rates may be underestimated.

Methotrexate was compared with placebo in a double-blind RCT that lasted 6 months. Among the 86 patients in the methotrexate group, 3% dropped out due to adverse events, 12% reported a gastrointestinal event, 7% reported pain, and 35% had a laboratory abnormality. No patients dropped out due to adverse events in the placebo arm. Sulfasalazine was compared with placebo in a good-quality, 6-month RCT. Of the 35 patients in the sulfasalazine arm, 29% dropped out due to adverse events. Reported events included gastrointestinal (29%), dermatologic (26%), neurologic (26%), and hematologic (6%) abnormalities. In addition, 6% of patients treated with sulfasalazine had elevated liver enzymes, and 4% had other laboratory abnormalities. All of the reported rates of adverse events were higher for the sulfasalazine group than the placebo group.
In a good-quality randomized study (n = 62) comparing abatacept with placebo, no adverse events were reported for either group. For anakinra, a 16-week study judged to be fair quality which changed from a study of efficacy to one reporting safety outcomes, found that 6 of 25 patients (24%) who received anakinra had gastrointestinal events, 8% had dermatologic events, 12% had fever, 6% reported pain, and 28% had other adverse events in the anakinra arm. None of the adverse events were considered serious, and these rates were reported as “similar” for the placebo group except for 10 patients (40%) who reported dermatologic events compared with 2 patients in the anakinra group.

Etanercept was compared with placebo in 1 good-quality study of children with polyarticular JIA (n = 25). Gastrointestinal events were reported in 4% of patients in the treatment arm, and there were no dropouts due to adverse events. Another fair-quality study that evaluated the safety of etanercept for the treatment of uveitis reported unspecified infection in 5 of 7 patients (71%) who received etanercept versus 3 of 5 patients (60%) who received placebo.

Infliximab plus methotrexate was compared with placebo plus methotrexate in a fair-quality multicenter, international RCT with an open-label extension. The study reported outcomes inconsistently, the nature of the serious adverse events was not specified, and reporting of adverse events was insufficient for comparison of infliximab versus placebo. Infections were reported in 68.3% of 60 patients who received infliximab 3 mg per kg plus methotrexate over 52 weeks versus 64.9% of 57 patients who received 6 mg per kg infliximab plus methotrexate and 46.7% of 60 patient show received placebo plus methotrexate. Serious adverse events were reported in 5.0% of patients in the placebo group over 14 weeks and in 32% of patients in the infliximab group over 52 weeks. The 3 mg per kg dose was associated with a higher rate of serious adverse events, infusion reactions, and the formation of antibodies compared with the 6 mg per kg dose. Lower doses of infliximab have a less favorable safety profile, which sets a basis for using higher dosing rates in children compared with adults. Due to the chimeric nature of infliximab, a higher risk for infusion reactions and allergies has been found compared with other TNF-alpha inhibitors.

Tocilizumab was compared with placebo in a fair-quality 12-week double-blind RCT phase preceded by a 6-week run-in phase. There was a 5% dropout rate in each arm due to adverse events. Among the 20 patients in the tocilizumab group, 5% reported a gastrointestinal event, 10% reported a respiratory event, and 5% reported a mononucleosis infection.

Other events associated with DMARD therapy, which were infrequently reported, included asthenia, malaise, hostility, and taste disturbance. DMARD use may have been associated with 1 death, which was reported in a girl on immunosuppressive therapy with cyclosporine A and methotrexate. At age 53 months, she died of Legionella pneumonia. Her autopsy revealed previously undiagnosed stage IV lymphoma. Studies included in the AHRQ review reported 10 cases of cancer, including 7 lymphomas. For studies comparing etanercept plus methotrexate with etanercept, there were 2 cases of thyroid carcinoma, 1 case of yolk sac carcinoma, and 2 cases of lymphoma. Among patients who had been treated with infliximab, etanercept, and methotrexate, 2 cases of lymphoma were reported. Three cases of lymphoma were reported in studies in which patients were treated with methotrexate alone. Aside from these cases of cancer reported among the several thousand patients who participated in the studies included in the AHRQ review, there was no clear evidence of a high incidence or prevalence of any serious adverse event associated with DMARDs.

In a search of the U.S. FDA Adverse Event Reporting System through April 2008, Diak et al. identified 48 cases of malignancies in people 22 years or younger who were treated with the TNF-alpha inhibitors infliximab, etanercept, or adalimumab. Half of these cases were lymphomas, with the majority (88%) involving the concomitant use of other immunosuppressants. From a search of clinical trials and global safety databases, McCroskery et al. identified 15 confirmed and 3 potential malignancies in children with JIA who were treated with etanercept. The confirmed cases included 7 lymphomas. The size of the population from which these cases were identified was not reported; thus, the researchers were not able to accurately estimate event rates or compare them to the baseline event rates for the population not exposed to TNF-alpha inhibitors.

Effectiveness and Safety of DMARDs for Various Categories of JIA

The Duke EPC investigators devised key question 4 in order to assess the comparative effectiveness of different DMARDs for children with various categories of JIA (Table 2). IL-1 inhibitors, including anakinra, rilonacept, and canakinumab, are mainly used for treating systemic JIA, while IL-6 inhibitors such as tocilizumab are more effective at treating systemic JIA and can be used to treat polyarticular JIA. The investigators reasoned that treatment outcomes may vary for patients with different disease types, stages, and severity. However, a thorough search of the literature revealed that the existing evidence is “insufficient” to evaluate the efficacy, effectiveness, or adverse events associated with DMARDs for children in different JIA categories. The lack of evidence is primarily attributable to the small numbers of subjects enrolled in existing studies and the complex nature of stratifying patients by disease category. The EPC investigators identified only 1 study to answer question 4 regarding the comparative effectiveness of the DMARDs in children in the different JIA categories. Woo et al. (2000) assessed the efficacy of methotrexate in 43 children with extended oligoarticular JIA and 45 children...
with systemic JIA.\textsuperscript{33} When the 2 JIA categories were analyzed separately, there were no significant differences in clinical outcomes, but Woo et al. did find significant clinical improvement with methotrexate treatment over this 12-month study when patients in the 2 JIA categories were combined. Safety data and adverse events were not reported by Woo et al. The Duke EPC investigators concluded that they could “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.”

### Assessment of JIA Outcomes Instruments

For key question 5, the Duke EPC investigators assessed the validity, reliability, responsiveness, and feasibility of the instruments used to measure outcomes of JIA treatments in clinical trials or practice settings. The investigators identified 34 studies (n = 14,381) that reported reliability, validity, and/or responsiveness of selected outcomes measures. Major findings from these psychometric evaluations are summarized in the following sections.

#### Measuring Reliability

Reliability measures the consistency of the instrument for assessing the outcome of interest. The EPC investigators evaluated 3 areas of reliability: reproducibility, inter-rater reliability, and internal consistency. Reproducibility, or test-retest reliability, measures the instrument’s ability to produce the same measurement repeatedly without changes in the patient’s status. A key finding, demonstrated in 5 studies, indicated that the CHAQ had high test-retest reliability, with correlations between 0.79 and 0.96.\textsuperscript{36-40} Moreover, strong correlations for inter-rater reliability were also observed for measures of functional status or disability on the CHAQ, CHQ physical score, PedsQL, and the PedsQL-RM.

#### Measuring Validity

Validity reflects how well an instrument measures what it is actually intended to measure. For some clinical outcomes measures, there is no reference standard for validity. However, for others such as joint inflammation, synovial biopsy is the reference standard. Therefore, validity was assessed according to the degree by which the measures correlated with other indicators of disease, including global assessments, articular counts, and scores from other validated instruments. The AHRQ review focused specifically on the validation of the instruments for children with JIA. The CHAQ correlated less well with AJC for children early in the course of disease than for children later in the course of disease (0.14 and 0.61, respectively). For children in the later stages of the disease, the CHAQ had a strong correlation with limited range of motion (0.76), but had lower correlations with the PGA (0.51).\textsuperscript{41} Weak correlations were generally observed between the CHAQ and indicators of disease activity, but moderately strong correlations were found between the CHAQ and other measures of functional status. Moderate correlations were found between the CHAQ and quality of life measures including the PedsQL (-0.62) and the PedsQL-RM (-0.63).\textsuperscript{42} Moderate correlations were also found between the CHAQ and the physical scale of the CHQ (PhS) (-0.58), and there was poor correlation with the psychosocial scale of the CHQ (PsS) (-0.25).\textsuperscript{43}

#### Measuring Responsiveness

Responsiveness is defined by reproducibility and the ability to register relevant changes in scores when a patient’s symptom status demonstrates improvements or deterioration. No universally recommended measure of responsiveness currently exists, and most rely on calculations of effect size, which is a unitless standardized measure of changes in assessment scores. The standardized response mean\textsuperscript{54} and the responsiveness index\textsuperscript{55,56} produce useful information for measuring response variance. Both of these statistics can be used to calculate effect size. Receiver operating characteristic (ROC) curves can be used to measure how well various changes in scale scores distinguish improved and unimproved patients. Effects sizes of 0.2 to 0.3 are considered small, 0.5 is a medium effect, and 0.8 is a relatively large effect.\textsuperscript{57} In analyses of 6 studies\textsuperscript{48-53} on the responsiveness of the CHAQ, effect sizes ranged from 0 to 0.5. The CHAQ was less responsive for patients with oligoarticular disease compared with polyarticular disease.\textsuperscript{58} PGA was the most responsive of the global assessment measures and joint count indices.\textsuperscript{50-52} Moderate to high responsiveness was also found for AJC and swollen joint count.\textsuperscript{51}

#### Directions for Future Research

As recognized by the Duke EPC investigators, many issues regarding the treatment of JIA remain unresolved. The limiting factors are often related to gaps and methodological limitations in the existing research. Thus, in concluding their comparative effectiveness review, the investigators call for future research that directly addresses the current shortcomings. Their suggestions include novel studies designed to provide data on long-term benefits and harms of JIA therapies. For valid outcomes, this line of research depends on the refinement of instruments that comprehensively, accurately, and reliably assess ongoing treatment responses.

Another critical issue for future research involves the heterogeneity of JIA, given its different definitions and disease categories. Thus, new studies should be designed to determine whether the effects of given therapies differ across disease subtypes. Of course, major challenges for such clinical trials include recruiting sufficient numbers of patients affected by the different categories of JIA and following patients over suf-
ficiently long time periods to account for characteristic fluctuations in disease activity and to measure long-term outcomes.

With regard to reaching conclusions through systematic reviews of the existing literature, a considerable drawback is the lack of consistency in study outcome measures. For example, among the studies included in the AHRQ review, there was notable variation in laboratory measures of inflammation as well as inconsistent assessment of AJCs, incidence of flares, and quality of life. The EPC investigators also propose new studies to:

- Determine the comparative effectiveness of specific DMARDs that are characterized by unique mechanisms of action (e.g., TNF-alpha inhibitors vs. IL-6 receptor antagonists)
- Compare the benefits and risks of DMARDs for patients at various points along the disease spectrum (e.g., at presentation, after failing conventional treatment)
- Identify the comparative effects of DMARDs on specific health conditions associated with JIA, including uveitis and macrophage activation syndrome
- Assess the incidence of treatment-related adverse events over long periods, through prospective cohort designs

In addition to these ideas for future studies, the EPC investigators suggest the establishment of JIA registries that collect outcomes data for patients treated with conventional therapies and DMARDs.

Current research on JIA is unfortunately insufficient to determine the rates and types of adverse events that can occur in patients treated with DMARDs and conventional therapies. The effects of JIA place a tremendous burden on the patient, family, and society as a whole. Ongoing research to determine the most effective outcome measures, laboratory biomarkers, and treatment interventions for JIA will guide physicians and other health care providers in making informed clinical decisions.

While the current research is a valid starting point for identifying the most effective and safe treatment options for children with JIA, other factors must be considered when making treatment decisions for individual patients. These considerations include, but are not limited to JIA category, disease severity, disease duration, prognostic factors, age, drug toxicities, drug safety monitoring, use of physical and/or occupational therapy, previous drug failures, multi-drug regimens, route of drug administration, access to medications, etc. A recommended treatment algorithm that attempts to account for many of these considerations was recently proposed by the ACR. However, with such complexities in therapeutic decision making, the care of children with JIA is best done directly by, or with guidance from, a health care provider with experience and/or training in caring for patients with JIA, such as a pediatric rheumatologist.

Conclusions

The AHRQ review on DMARDs used to treat children with JIA found, with a moderate strength of evidence, that biologic DMARDs decreased the risk of flares in randomized discontinuation trials for children who had responded to a biologic DMARD. Among the nonbiologic DMARDs, methotrexate was found superior to conventional therapy based on 2 RCTs with 215 patients. There were insufficient data to evaluate the effect of DMARDs on radiologic progression.

A low strength of evidence shows inconsistent improvement in health status associated with treatment of JIA with DMARDs. Direct comparisons of nonbiologic DMARDs (penicillamine, hydroxychloroquine, sulfasalazine, leflunomide, and methotrexate) demonstrated similar efficacy for health status; however the precision of measurements of changes in health status between treatment arms was insufficient to detect a difference. One poor quality RCT found etanercept to be similar to infliximab in health status. Low strength of evidence from 4 RCTs and 1 cohort study shows that ESR as a laboratory measure of inflammation is inconsistently associated with response to treatment with DMARDs.

The evidence was rated insufficient to determine if either the rates and types of adverse events differ among the various DMARDs or if there is a difference in these outcomes in treatment across the various categories of JIA. The totality of evidence available from only 3 RCTs shows that the rate and types of adverse events did not differ between DMARDs (i.e., penicillamine vs. hydroxychloroquine and leflunomide vs. methotrexate), but valid comparisons were not possible because of high variability in the determination and reporting of adverse events across the studies. There were no RCTs that compared a DMARD to conventional treatment, and the 13 trials for comparison of a DMARD to placebo showed the rate of adverse events to be similar for DMARDs and placebo except 1 study that reported 32% of patients experienced adverse events for the combination of infliximab with methotrexate versus 5% for placebo and a 35% rate of laboratory abnormalities with the combination versus 13% for placebo. Data derived from adverse event reporting databases suggest that cancer, particularly lymphoma, may be related to exposure to TNF-alpha inhibitors. For the question of safety and rate of adverse events for the DMARDs among the various JIA categories, no studies were found that provided reliable evidence; in the only RCT that addressed the question, methotrexate was similar to placebo in 2 JIA categories (extended oligoarticular and systemic).

The strength of the evidence was also found to be insufficient to answer the question regarding validity, reliability, responsiveness, and feasibility of the clinical outcome measures for childhood JIA used in clinical practice and clinical trials. No instrument or outcome measure was found superior to another in measuring disease activity, functional status, or responsiveness to changes in disease state. The ACR Pediatric...
30 is a combined measure that includes articular indices, functional status, laboratory measures, and global assessments, and accounts for the various measures most commonly used to assess JIA disease activity. However, the ACR Pediatric 30 is a relative measure of disease activity and not a measure of current disease state.

The ratio of benefit versus harm in the treatment of JIA with DMARDs cannot be determined from the available evidence. Methotrexate is the most studied DMARD and has a moderate strength of evidence of efficacy. Although the available evidence suggests that the risk of harm associated with methotrexate is similar to placebo, 1 study reported more adverse events compared with placebo for methotrexate used in combination with infliximab. Evidence of efficacy from randomized discontinuation for the biologic DMARDs is offset by the unknown safety of these drugs in children, particularly in long-term use. There is insufficient evidence of efficacy to support the use of one DMARD over another.

Summary of AHRQ’s Comparative Effectiveness Review of Disease-Modifying Antirheumatic Drugs for Children with Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) affects 300,000 children in the United States. However, the direct cost of JIA in 1992 was estimated at $285 million with a mean annual direct cost of $7,905 per child. With the introduction of high-cost treatments, such as the biologic disease-modifying antirheumatic drugs (DMARDs), the costs of managing JIA have likely increased significantly in the last 30 years. Children with arthritic conditions are also seen by physician offices and emergency rooms numerous times per year. Additionally, most children with JIA will continue to have symptoms and disease activity into adulthood. Although patients with JIA represent a relatively small portion of the population, these are high-cost, high-utilizing patients who will have increased costs from childhood well into adulthood. Therefore, managed care organizations can play an important role in providing optimal clinical care, controlling costs, and ensuring appropriate use of the medications used to treat JIA.

This AHRQ systematic review examined studies comparing the efficacy and safety of nonbiologic DMARDs, biologic DMARDs, and conventional therapies in the treatment of JIA. However, the authors of the review recognize the paucity of data in this area. The authors considered there to be insufficient evidence regarding the comparison of efficacy between biologic and nonbiologic DMARDs to conventional therapy and were unable to provide a meta-analysis of the results. Instead the results of individual studies are reported. Additionally, the authors also found insufficient evidence regarding the comparison of efficacy between DMARDs to determine if any drug class was associated with better outcomes. The safety of DMARDs and conventional therapies was also reported, but due to inconsistent methodologies among studies, the authors recommended interpreting the results with caution and thus reported the results for individual studies.

Unfortunately due to limitations in the current literature, this systematic review is unable to provide direction to managed care organizations with regard to the comparative effectiveness of drug classes to aid in formulary and coverage decisions. However, the review does provide an important starting point for these decisions by synthesizing the results of many individual studies into a single report and grading the evidence found. This review also underscores the need for decision makers to carefully evaluate the literature before making coverage decisions, especially when little evidence is available. Finally, this review highlights the need for high-quality comparative effectiveness research for JIA treatments, especially with regard to long-term outcomes.

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