Medical Treatment of Juvenile Idiopathic Arthritis

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Ronald M. Laxer, MD, FRCP

Context The treatment of juvenile idiopathic arthritis (JIA) has changed markedly in the last 15 years. Many children with JIA are not treated by pediatric rheumatologists.

Objective To review the best evidence for the treatment of JIA.

Data Sources English-language trials of JIA between 1966 and 2005 were searched using MEDLINE, EMBASE, the Cochrane database, and abstracts from recent rheumatology and pediatric scientific meetings.

Study Selection Randomized controlled trials and open studies including at least 10 patients for medications without controlled trials.

Data Extraction For studies after 1997, the American College of Rheumatology Pediatric 30 outcome measure was used to define patients as responders. For older studies, the primary response outcome measure defined by the authors was used.

Data Synthesis Thirty-four controlled studies were identified. Nonsteroidal anti-inflammatory drugs are effective only for a minority of patients, mainly those with oligoarthritis. Intra-articular corticosteroid injections are very effective for oligoarthritis. Methotrexate is effective for the treatment of extended oligoarthritis and polyarthritis and less effective for systemic arthritis. Sulfasalazine and leflunomide may be alternatives to methotrexate. Antitumor necrosis factor medications are highly effective for polyarticular course JIA not responsive to methotrexate but are less effective in systemic arthritis.

Conclusions Despite many advances in the treatment of JIA, there is still a lack of evidence for the optimal treatment of systemic and enthesitis-related arthritis.

METHODS

Data Sources
A literature search was performed for English-language clinical trials in JIA, with an emphasis on randomized trials. We used MEDLINE, EMBASE, and Cochrane and systematic reviews to identify trials from 1966 to 2005 and reviewed abstracts from the 2003 to 2004 major rheumatology and pediatric meetings. Besides JIA, we used other terms of chronic arthritides of childhood and searched all drugs used to treat inflammatory arthritides (list available on request). A total of 279 studies were identified including 34 randomized and 28 double-blinded trials. Fourteen controlled trials were for nonsteroidal anti-inflammatory drugs (NSAIDs), 14 for disease-modifying antirheumatic drugs (DMARDs) or immunosuppressive medications or systemic corticosteroids, 3 for intra-articular corticosteroid injections, and 3 for biologic agents.
modifying agents (Table 2, Table 3, Table 4, Table 5). For medications without controlled studies, open trials or series with at least 10 patients were reviewed. Meta-analysis was not performed since for most medications except NSAIDs, only 1 controlled trial was done for a specific JIA subtype. Furthermore, for medications with more than 1 study, the comparison group was usually an active control, the study designed as an equivalence study, and the outcomes varied significantly.

Outcome Measures

We used the validated consensus outcome measures of the American College of Rheumatology (ACR) Pediatric 30 defining patients as responders or nonresponders, which were developed in 1997 (Box). For older trials, we used the responder measure defined by the authors. There was a large variance in those outcome definitions.

### Table 1. Subtypes of Juvenile Idiopathic Arthritis*

<table>
<thead>
<tr>
<th>Juvenile Idiopathic Arthritis Subtype</th>
<th>Proportion of Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic arthritis (starts with spiking fever, rash)</td>
<td>10-20</td>
</tr>
<tr>
<td>Oligoarthritis (≤4 joints in first 6 mo)</td>
<td>40-60</td>
</tr>
<tr>
<td>Persistent oligoarthritis course</td>
<td></td>
</tr>
<tr>
<td>Extended polyarticular course</td>
<td></td>
</tr>
<tr>
<td>Polyarthritis rheumatoid factor negative (≥4 joints in first 6 mo)</td>
<td>20-25</td>
</tr>
<tr>
<td>Polyarthritis rheumatoid factor positive</td>
<td>5-10</td>
</tr>
<tr>
<td>Enthesitis-related arthritis (formerly called spondyloarthropathy)</td>
<td>Undetermined</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>5</td>
</tr>
<tr>
<td>Other (fits none or &gt;1 category)</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>

*Adapted from Petty et al.*

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**Treatments**

**Rationale for the Current Treatment Approach.** Until 1990, treatment was based on the pyramid approach initially using various NSAIDs and corticosteroids and gradually advancing to other medications. Studies, however, have indicated that previous assumptions on the course and outcome of JIA were incorrect. Radiologic joint damage, thought to occur late in the disease course, occurs in most patients with systemic arthritis and polyarthritis within 2 years and in oligoarthritis within 5 years. Earlier cartilage damage was demonstrated using magnetic resonance imaging.

The assumption that JIA will usually resolve by adulthood is incorrect. Between 50% and 70% of patients with systemic arthritis or polyarthritis and 40% to 50% of patients with oligoarthritis continue to have active disease in adulthood. Between 30% and 40% of patients have significant long-term disabilities including unemployment, and between 25% and 50% need major surgery, including joint replacement. Patients with oligoarthritis frequently develop muscle atrophy. JIA is associated with a mortality rate of 0.4% to 2% occurring mainly in patients with systemic arthritis, with amyloidosis and the macrophage activation syndrome being the main causes.

Poor outcome predictors can help determine patients requiring early aggressive therapy. Patients with polyarthritis and positive rheumatoid factor, antibodies to cyclic citrullinated peptides, the presence of HLA-DR4, nodules, and early onset symmetric small joint involvement have a poor prognosis. Patients with systemic arthritis who are corticosteroid dependent for control of systemic symptoms and have a platelet count of more than $600 \times 10^9/\mu L$ after 6 months of disease, or who have a G-C macrophage migration inhibitory factor gene polymorphism have a poor outcome.

**Nonsteroidal Anti-inflammatory Drugs.** None of the studies of aspirin or...
**Table 2. Controlled Clinical Trials of NSAIDs in Juvenile Idiopathic Arthritis**

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Study Type</th>
<th>Length of Treatment, wk</th>
<th>Type of Arthritis</th>
<th>Definition of Response</th>
<th>Daily Medication</th>
<th>Responders, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levinson et al. 1977</td>
<td>107</td>
<td>Randomized, double-blind, multicenter</td>
<td>12</td>
<td>All types</td>
<td>% Improvement in index of active joints</td>
<td>Tolmetin 15-30 mg/kg Aspirin 50-100 mg/kg</td>
<td>25 26</td>
<td>Similar adverse effects</td>
</tr>
<tr>
<td>Makela, 1977</td>
<td>18</td>
<td>Randomized, double-blind, crossover</td>
<td>8 for each drug</td>
<td>Not stated</td>
<td>Physician preference for drug</td>
<td>Naproxen 6.5 mg/kg Aspirin 60 mg/kg</td>
<td>46 27</td>
<td>Equal efficacy in 27% of patients</td>
</tr>
<tr>
<td>Bhettay and Thomson, 1978</td>
<td>30</td>
<td>Randomized, double-blind, crossover</td>
<td>2 for each drug</td>
<td>All types</td>
<td>Patient preference for drug</td>
<td>Ketoprofen 50 or 100 mg Indomethacin 50 or 100 mg</td>
<td>25 75*</td>
<td>Dose based on weight; no difference in adverse effects</td>
</tr>
<tr>
<td>Brewer et al. 1982</td>
<td>99</td>
<td>Randomized, double-blind, multicenter</td>
<td>12</td>
<td>All types</td>
<td>Any improvement in physician global assessment</td>
<td>Fenoprofen 900-1800 mg/m² Aspirin 1500-3000 mg/m²</td>
<td>62 63</td>
<td>Dose increased after 4 wk; more patients discontinued aspirin due to adverse effects</td>
</tr>
<tr>
<td>Haapasaari et al. 1983</td>
<td>45</td>
<td>Randomized, double-blind</td>
<td>2</td>
<td>All types</td>
<td>Any improvement in 4-point physician global scale</td>
<td>Diclofenac 2-3 mg/kg Aspirin 50-100 mg Placebo</td>
<td>73* 50* 27</td>
<td>Significantly fewer adverse effects in diclofenac group vs aspirin</td>
</tr>
<tr>
<td>Kven et al. 1984</td>
<td>80</td>
<td>Randomized, double-blind</td>
<td>24</td>
<td>Oligoarthritis, polyarthritis</td>
<td>% Improvement in index of active joints</td>
<td>Naproxen 10 mg/kg Aspirin 75 mg/kg</td>
<td>39 22</td>
<td>More patients discontinued aspirin due to adverse effects</td>
</tr>
<tr>
<td>Bhettay 1986</td>
<td>30</td>
<td>Randomized, double-blind, crossover</td>
<td>3 for each drug</td>
<td>All types</td>
<td>Any improvement in physician global assessment</td>
<td>Sulindac 50, 75, or 150 mg Aspirin 1500, 2700, or 3600 mg</td>
<td>22 25</td>
<td>Dose determined by weight</td>
</tr>
<tr>
<td>Williams et al. 1986</td>
<td>47</td>
<td>Randomized, double-blind, multicenter, crossover</td>
<td>4 for each drug</td>
<td>Oligoarthritis, polyarthritis</td>
<td>Physician preference for drug</td>
<td>Naproxen 15 mg/kg Piroxicam 5, 10, 15, or 20 mg</td>
<td>24 26</td>
<td>Dose determined by weight</td>
</tr>
<tr>
<td>Garcia-Morteo et al. 1987</td>
<td>26</td>
<td>Randomized, double-blind</td>
<td>12</td>
<td>Polyarthritis</td>
<td>Any improvement in physician global assessment</td>
<td>Naproxen 12.5 mg/kg Piroxicam 5, 10, or 15 mg</td>
<td>38 67*</td>
<td>No significant differences by patient-parent assessment; dose determined by weight</td>
</tr>
<tr>
<td>Beat et al. 1988</td>
<td>28</td>
<td>Randomized, single-blind, crossover</td>
<td>4 for each drug</td>
<td>Oligoarthritis, polyarthritis</td>
<td>No change or any improvement in physician global assessment</td>
<td>Naproxen 10 mg/kg Diclofenac 2 mg/kg Tolmetin 25 mg/kg</td>
<td>89 89 86</td>
<td></td>
</tr>
<tr>
<td>Giannini et al. 1990</td>
<td>92</td>
<td>Randomized, double-blind, multicenter</td>
<td>12</td>
<td>All types</td>
<td>Any improvement in physician global assessment</td>
<td>Ibuprofen 30-40 mg/kg Aspirin 80-80 mg/kg</td>
<td>79 77</td>
<td>More adverse effects in aspirin group</td>
</tr>
<tr>
<td>Kiss et al. 2003 (abstract)</td>
<td>310</td>
<td>Randomized, double-blind, international, non-inferiority</td>
<td>12</td>
<td>Oligoarthritis, polyarthritis</td>
<td>ACR Pediatric 30</td>
<td>Rofecoxib 0.3 mg/kg (maximum 12.5 mg) Rofecoxib 0.6 mg/kg (maximum 25 mg) Naproxen 15 mg/kg</td>
<td>46 54 55</td>
<td>Only low dose rofecoxib group had significantly less gastrointestinal adverse effects</td>
</tr>
<tr>
<td>Gedalia et al. 2004 (abstract)</td>
<td>209</td>
<td>Randomized, double-blind, international, non-inferiority</td>
<td>12</td>
<td>Oligoarthritis, polyarthritis</td>
<td>ACR Pediatric 30</td>
<td>Naproxen 5-7.5 mg/kg† Meloxicam 0.125-0.25 mg/kg Meloxicam 0.25-0.375 mg/kg</td>
<td>4 wk 12 wk 4 wk 12 wk 4 wk 12 wk</td>
<td>Dose increased after 4 wk</td>
</tr>
<tr>
<td>Ruperto et al. 2005</td>
<td>225</td>
<td>Randomized, double-blind, international, non-inferiority</td>
<td>52</td>
<td>Oligoarthritis, polyarthritis</td>
<td>ACR Pediatric 30</td>
<td>Naproxen 10 mg/kg† Meloxicam 0.125 mg Meloxicam 0.25 mg</td>
<td>74 77 76</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** ACR, American College of Rheumatology; NSAID, nonsteroidal anti-inflammatory drug.

*Significant positive effect.
†Dosage is taken twice per day.
‡Percentage of responders is denoted at 4 weeks and at 12 weeks.

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**Table 3. Controlled Clinical Trials of Disease-Modifying Antirheumatic Medications, Systemic-Corticosteroids, and Other Medications in Juvenile Idiopathic Arthritis**

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient No.</th>
<th>Study Type</th>
<th>Length of Treatment, wk</th>
<th>Type of Arthritis</th>
<th>Definition of Response</th>
<th>Medication</th>
<th>Responders, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kvien et al, 1985</td>
<td>77</td>
<td>Randomized, open</td>
<td>50</td>
<td>Oligoarthritis, polyarthritis</td>
<td>50% Improvement in physician global assessment</td>
<td>Intramuscular gold 0.7 mg/kg per injection 0.15-0.2 mg/kg per d</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Kvien et al, 1985</td>
<td>72</td>
<td>Randomized, open</td>
<td>50</td>
<td>Oligoarthritis, polyarthritis</td>
<td>50% Improvement in physician global assessment</td>
<td>Hydroxychloroquine 5 mg/kg per d Intramuscular gold 0.7 mg/kg per injection 0.15-0.2 mg/kg per d</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Prieur et al, 1985</td>
<td>74</td>
<td>Randomized, double-blind, multicenter</td>
<td>26</td>
<td>Oligoarthritis, polyarthritis</td>
<td>Any improvement in physician global assessment</td>
<td>Hydroxychloroquine 6 mg/kg/d D-penicillamine 0.15-0.2 mg/kg per d</td>
<td>55*</td>
<td></td>
</tr>
<tr>
<td>Brewer, et al, 1986</td>
<td>162</td>
<td>Randomized, double-blind, international</td>
<td>52</td>
<td>Polyarthritis</td>
<td>Composite index†</td>
<td>Placebo</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Kvien et al, 1986</td>
<td>32</td>
<td>Randomized, double-blind</td>
<td>16</td>
<td>All types</td>
<td>25% Improvement in index of active joints</td>
<td>Azathioprine 2-2.5 mg/kg per d</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Giannini et al, 1990</td>
<td>231</td>
<td>Randomized, double-blind, international</td>
<td>26</td>
<td>All types, &gt;3 active joints</td>
<td>Composite index†</td>
<td>Oral gold 0.15-0.2 mg/kg per d</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Hoza et al, 1991</td>
<td>39</td>
<td>Randomized, double-blind</td>
<td>26</td>
<td>Oligoarthritis, polyarthritis</td>
<td>Any improvement in 4 criteria: active joints, pain, morning stiffness, erythrocyte sedimentation rate, functional capacity</td>
<td>Sulfasalazine 20-30 mg/kg per d Chloroquine 3-4 mg/kg per d</td>
<td>48</td>
<td>More adverse reactions with sulfasalazine</td>
</tr>
<tr>
<td>Giannini et al, 1992</td>
<td>127</td>
<td>Randomized, double-blind, international</td>
<td>26</td>
<td>All types, &gt;3 active joints</td>
<td>Composite index†</td>
<td>Oral methotrexate 5 mg/m² body surface area per wk</td>
<td>32</td>
<td>Significant effect only of methotrexate 10 mg/m²</td>
</tr>
<tr>
<td>Picco et al, 1996</td>
<td>22</td>
<td>Randomized, open</td>
<td>26</td>
<td>Systemic</td>
<td>Decrease in daily oral corticosteroid dose at 6 mos</td>
<td>Intravenous methylprednisolone 5 mg/kg per day for 3 days then 2.5 mg/kg per day for 5 days then oral 1 mg/kg per d</td>
<td>74*</td>
<td>Significant less cumulative dose in initial intravenous group</td>
</tr>
<tr>
<td>Van Rossum et al, 1998</td>
<td>69</td>
<td>Randomized, double-blind, multicenter</td>
<td>24</td>
<td>Oligoarthritis, polyarthritis</td>
<td>Pediatric ACR 30§</td>
<td>Sulfasalazine 50 mg/kg/d, maximum 2 g per d</td>
<td>44*</td>
<td>More sulfasalazine adverse effects</td>
</tr>
<tr>
<td>Woo et al, 2000</td>
<td>88</td>
<td>Randomized, double-blind, crossover, multicenter</td>
<td>16</td>
<td>Systemic or oligoarthritis with polyarthritis course</td>
<td>ACR Pediatric 30§</td>
<td>Oral methotrexate 15-20 mg/m² per wk</td>
<td>25</td>
<td>Methotrexate dose allowed to increase after 2 mo</td>
</tr>
<tr>
<td>Burgos-Vargas et al, 2002</td>
<td>33</td>
<td>Randomized, double-blind</td>
<td>26</td>
<td>Enthesitis-related</td>
<td>Reduction in active joints</td>
<td>Sulfasalazine 30-60 mg/kg per d, maximum 2000 mg per d</td>
<td>46</td>
<td>Significantly more improvement in sulfasalazine group by physician and patient assessment</td>
</tr>
<tr>
<td>Rupertto et al, 2004</td>
<td>80‡</td>
<td>Randomized, open international</td>
<td>26</td>
<td>Polyarthritis course</td>
<td>ACR Pediatric 30</td>
<td>Parenteral methotrexate 30 mg/m² per wk</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Silverman et al, 2005</td>
<td>94</td>
<td>Randomized, double-blind, multi-center</td>
<td>16</td>
<td>Polyarthritis course</td>
<td>Pediatric ACR 30</td>
<td>Leflunomide 10 mg every other day to 20 mg per d</td>
<td>68</td>
<td>Leflunomide dose per weight; methotrexate maximum dose 25 mg/wk</td>
</tr>
</tbody>
</table>

Abbreviation: ACR, American College of Rheumatology.

*Significant positive effect.
†Composite index: ≥25% reduction in active joints and improvement in physician and patient global assessment.
‡80 Patients not responsive to oral methotrexate 10 mg/m²/week (out of 595).
§Without functional measure.

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other NSAIDs were placebo controlled, since it is ethically difficult to perform placebo controlled studies in children, particularly for drugs benefiting adults (Table 2). In a summary of studies, only about 25% to 33% of the patients, mainly those with oligoarthritis, showed a significant response to NSAIDs. A 4- to 6-week trial of an individual NSAID is necessary to assess its efficacy. Since NSAIDs are not disease modifying, they are used more to treat pain, stiffness, and the fever associated with systemic arthritis. No individual NSAID has been shown to have a clear advantage over others in treating arthritis or the fever associated with systemic arthritis. The need to administer aspirin 3 times per day, to monitor serum levels, the greater frequency of liver enzyme abnormalities, and the possible association of Reye syndrome with salicylates have largely resulted in other NSAIDs replacing aspirin.

NSAIDs approved by the US Food and Drug Administration for use in JIA include tolfenin, naproxen, ibu-

### Table 4. Controlled Clinical Trials of Intra-articular Corticosteroid Injections in Juvenile Idiopathic Arthritis

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Study Type</th>
<th>Length of Follow-up</th>
<th>Type of Arthritis</th>
<th>Definition of Response</th>
<th>Medication</th>
<th>Responders, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balogh and Ruzsony</td>
<td>23</td>
<td>Randomized, double-blind</td>
<td>6 wk</td>
<td>Oligoarthritis</td>
<td>Difference in knee circumference</td>
<td>Triamcinolone hexacetonide†</td>
<td>−1.7 cm*</td>
<td>Only knees studied</td>
</tr>
<tr>
<td>Zulian et al, 2003</td>
<td>85 (130 joints)</td>
<td>Randomized, blinded assessment</td>
<td>24 mo</td>
<td>Oligoarthritis</td>
<td>≥60% decrease in articular score</td>
<td>Triamcinolone hexacetonide†</td>
<td>6 mo</td>
<td>81* Dose dependent on joint size</td>
</tr>
<tr>
<td>Zulian et al, 2004</td>
<td>37 (43 paired joints with inflammation)</td>
<td>Randomized, double-blind</td>
<td>24 mo</td>
<td>Oligoarthritis, polyarthritis</td>
<td>% Joints without inflammation</td>
<td>Triamcinolone hexacetonide†</td>
<td>6 mo</td>
<td>90*</td>
</tr>
</tbody>
</table>

*Significant positive effect.
†Dose not stated.

### Table 5. Controlled Clinical Trials of Biologic-Modifying Medications in Juvenile Idiopathic Arthritis

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients</th>
<th>Study Type</th>
<th>Length of Treatment, wk</th>
<th>Type of Arthritis</th>
<th>Definition of Response</th>
<th>Medication</th>
<th>Responders/ Flare, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverman et al, 1994</td>
<td>31</td>
<td>Randomized, double-blind, multicenter</td>
<td>26</td>
<td>Systemic</td>
<td>Physician global assessment</td>
<td>Intravenous immunoglobulin 1.5 g/kg per mo Placebo</td>
<td>50</td>
<td>In first 2 mo drug was given biweekly; small study power</td>
</tr>
<tr>
<td>Giannini et al, 1996</td>
<td>19§</td>
<td>Randomized, double-blind, withdrawal, multicenter</td>
<td>16</td>
<td>Polyarthritis</td>
<td>Composite index†</td>
<td>Intravenous immunoglobulin 2 g/kg per mo Placebo</td>
<td>20§</td>
<td>Small study power</td>
</tr>
<tr>
<td>Lovell et al, 2000</td>
<td>51†</td>
<td>Randomized, double-blind, withdrawal, multicenter</td>
<td>16</td>
<td>Polyarthritis-course</td>
<td>Modified ACR Pediatric 30 for flare</td>
<td>Subcutaneous etanercept 0.4 mg/kg per dose twice weekly Placebo</td>
<td>28†</td>
<td></td>
</tr>
</tbody>
</table>

*Significant positive effect.
†Dose not stated.
§19 responders in 2-month open phase were randomized from 25 patients.
†19 responders in 3-month open phase were randomized from 69 patients.
| Abbreviations: ACR, American College of Rheumatology. |

### Box. Validated Outcome Measures for Juvenile Idiopathic Arthritis Trials

**Active joint count** (joints with swelling or with limitation of motion and tenderness/pain on motion)

**Joints with limited range of motion**

Parent/Patient global assessment (measured on 0-10 visual analog scale)

Physician global assessment (measured on 0-10 visual analog scale)

Laboratory measure of inflammation (erythrocyte sedimentation rate, C-reactive protein)

Functional assessment (Childhood Health Assessment Questionnaire)

A patient is considered to have responded if there has been an improvement in at least 3 variables by at least 30% and worsening in not more than one variable by more than 30%.

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Figure 3. Ankle Showing Adverse Effect of Corticosteroid Injection

Right ankle demonstrating atrophy and hypopigmentation secondary to corticosteroid injection.

profen, and rofecoxib (rofecoxib has since been removed from the market due to cardiovascular adverse effects in adults). Liquid preparations of naproxen and ibuprofen are also available. Other NSAIDs that have undergone controlled studies include diclofenac, ketoprofen, indomethacin, piroxicam, fenoprofen, sulindac, and meloxicam (Table 2). Comparative efficacy of nabumetone was addressed and there are no case reports of these events in JIA. Only 2 NSAID studies (for naproxen and meloxicam) prospectively followed JIA patients for at least 6 months.

Corticosteroids. Due to many deleterious effects, especially on bone and growth, pediatric rheumatologists try to minimize systemic use of corticosteroids for JIA. There is no evidence that systemic corticosteroids are disease modifying. The main indications are severe fever, serositis, and the macrophage activation syndrome in systemic arthritis or as a bridging medication until other medications become effective. In some patients, periodic intravenous pulses of corticosteroids (30 mg/kg per dose, maximal 1 g) are used instead of high-dose daily oral corticosteroids, although there are no controlled studies showing fewer adverse effects in children. A retrospective series of 20 patients with systemic arthritis reported on the use of high-dose alternate-day corticosteroids as an alternative to daily corticosteroids with equal efficacy and fewer adverse reactions. One controlled study showed that the use of intravenous pulses of corticosteroids in the first week of treating systemic arthritis resulted in lower daily and cumulative doses at 6 months, when compared with initial oral doses of corticosteroids (Table 3).

There is better evidence for the efficacy of intra-articular injections of corticosteroids, particularly in patients with oligoarthritis (Table 4). Studies have shown that as many as 70% of patients with oligoarthritis do not have reactivation of disease in the injected joint for at least 1 year and 40% for more than 2 years. Radiographic and magnetic resonance imaging studies have shown a marked decrease in synovial volume after injection without deleterious effects on the cartilage. There were significantly fewer patients with leg length discrepancies in a practice advocating repeated early intra-articular corticosteroid injections when compared with a practice rarely employing intra-articular injections. The efficacy is less in other JIA subtypes, especially systemic arthritis patients with the G-C macrophage migration inhibitory factor gene polymorphism.

Adverse effects are few and most often are the development of periarticular subcutaneous atrophy (Figure 3). This can often be prevented by injecting small amounts of saline into the joint and applying pressure following the injection. Repeated injections to an individual joint were not found to be associated with joint or cartilage damage. Asymptomatic calcifications are occasionally found after injections. In one series examining the outcome of hip injections, aseptic necrosis did not occur. The long-acting triamcinolone hexacetonide is more effective and has a longer effect than other forms of injectable corticosteroids (Table 4). Younger children or children needing multiple joint injections usually require sedation.

Methotrexate. Methotrexate is the treatment cornerstone for most patients with polyarthritis (Table 3). An open randomized study showed that increasing the dose of methotrexate to 15 mg/m² per week and giving methotrexate parenterally was effective for most patients not responsive to 10 mg/m² per week. There was no additional advantage in giving higher doses up to 30 mg/m² per week. The greatest efficacy of methotrexate was seen in patients with extended oligoarthritis, while in a randomized study no significant effect was found in patients with systemic arthritis. Methotrexate may exhibit a disease-modifying effect as the radiologic damage progression rate was decreased in 2 small uncontrolled series.

It is not clear when a patient can stop taking methotrexate because the disease will flare in as many as 60% of the patients after discontinuing methotrexate. One study found that continuing methotrexate for more than 1 year of inactive disease was associated with a lower rate of flare, while another did not find differences between patients who discontinued methotrexate 3 months after disease inactivity vs 1
year.\textsuperscript{89} The level of myeloid-basic protein 14 when methotrexate was discontinued was a better predictor of flare.\textsuperscript{89} Nearly 90\% of patients respond when methotrexate is restarted.\textsuperscript{88,89}

Since food decreases the bioavailability of methotrexate, it is advised to give methotrexate on an empty stomach.\textsuperscript{91} At doses of 10 mg/m\textsuperscript{2} per week, there is no difference in the efficacy of oral or parenteral methotrexate but the latter is better tolerated.\textsuperscript{92,93} Methotrexate at greater doses is usually given by subcutaneous or intramuscular injection, since oral methotrexate is not absorbed well at doses equal to or above 12 mg/m\textsuperscript{2}.\textsuperscript{94}

Methotrexate should be administered with folic acid 1 mg per day, or folinic acid, 25\% to 50\% of the methotrexate dose, given once weekly the day after methotrexate. A controlled study of folic acid and a retrospective study of folinic acid found decreased occurrences of nausea, oral ulcerations, and perhaps liver enzyme abnormalities without decreasing the efficacy of methotrexate.\textsuperscript{95,96}

Nausea and other gastrointestinal symptoms are frequent. Management strategies include taking methotrexate before bed, switching the administration from oral to parenteral, and using antiemetics.\textsuperscript{97} Some children develop a psychologic aversion to methotrexate that can be alleviated by teaching relaxation or self-hypnosis techniques.

Tests to monitor complete blood cell counts, liver enzymes, and renal function are recommended, although the optimal frequency of testing is unclear. A recent study reported that tests at 3-month intervals at doses up to 15 mg/m\textsuperscript{2} per week detected significant hepatotoxicity.\textsuperscript{98,99} While mild elevations of liver enzymes occur frequently, no cases of severe, irreversible liver fibrosis have been reported in JIA.\textsuperscript{99,100} Routine liver biopsies are not recommended. Persistent liver enzyme abnormalities and obesity are associated with more significant histology changes, including mild fibrosis, and liver biopsies should be considered in those patients.\textsuperscript{101} Pulmonary toxicity is very rare in children and pulmonary function was normal in patients with JIA on long-term methotrexate.\textsuperscript{102,103} Nodulosis has rarely been reported.\textsuperscript{104,105} Very few severe infections have been reported in children. Children should avoid live vaccinations while using methotrexate and annual influenza vaccine is recommended. If possible, children should receive varicella vaccine prior to starting methotrexate. Rare cases of Hodgkin and non-Hodgkin lymphomas have been reported in children treated with methotrexate.\textsuperscript{106-109} However, current data do not suggest that the rate of malignancies is greater than in the general child population.

Other Disease-Modifying Antirheumatic Drugs and Immunosuppressive Medications

Most controlled studies in children did not find hydroxychloroquine, oral gold, or D-penicillamine to be significantly effective in the treatment of JIA, although one study using less rigorous outcome measures found that D-penicillamine was more effective than placebo in the treatment of oligoarthritis and polyarthritis.\textsuperscript{30-33,35,110-112} One study did not find parenteral gold to be more effective than D-penicillamine or hydroxychloroquine.\textsuperscript{31}

Most studies of sulfasalazine were not controlled.\textsuperscript{113} One controlled study showed that sulfasalazine is effective in the treatment of oligoarthritis and polyarthritis.\textsuperscript{36} However, in a small placebo-controlled study of juvenile spondyloarthropathy,\textsuperscript{114} and a study comparing sulfasalazine with chloroquine in oligoarthritis and polyarthritis,\textsuperscript{36} no significant differences were found. In many of the open studies, sulfasalazine was most effective in boys older than age 9 years and adolescents aged 13 to 17 years with oligoarthritis,\textsuperscript{113} representing, perhaps, children with enthesitis-related arthritis. Adverse reactions were frequently reported, especially rashes, gastrointestinal symptoms, and leukopenia, and sulfasalazine was discontinued in nearly one third of the patients.\textsuperscript{30,113} Adverse effects may be especially severe in patients with systemic arthritis.\textsuperscript{113}

In a controlled study comparing leflunomide with methotrexate for patients with polyarthritis, significantly more responders were found in the methotrexate group, although high response rates were also found with leflunomide.\textsuperscript{82} Most of the patients responsive to leflunomide maintained their response in a 2-year open label extension study.\textsuperscript{113} No significant differences in adverse effects were found. A controlled study of azathioprine did not find a significantly greater efficacy than placebo.\textsuperscript{34} There are no studies of nivocycine use in JIA.

There are no controlled studies of cyclosporin A in JIA. Small series have shown cyclosporin A to be efficacious in some patients refractory to methotrexate.\textsuperscript{116,117} Cyclosporin A may be more beneficial for fever control and corticosteroid dose reduction than for the treatment of arthritis in systemic arthritis and may be especially effective in patients with the macrophage activation syndrome.\textsuperscript{117,118} There were many adverse effects, especially renal, associated with cyclosporine.

One large open series showed chlorambucil to be beneficial in patients with refractory JIA, especially those with amyloidosis, but the high mortality rate (6\%), including the development of leukemia, precludes using the drug other than as a last resort.\textsuperscript{119,120}

An open series of 13 patients found that thalidomide was effective in the treatment of refractory systemic arthritis, both for systemic features and arthritis.\textsuperscript{121} No significant adverse effects were noted. Besides the teratogenic effect, careful observation for the development of peripheral neuropathy is necessary.

There are no controlled studies of combination DMARD therapy in JIA. In a series of 17 patients with polyarthritis refractory to methotrexate, treated with methotrexate and cyclosporin A, 8 patients (47\%) met the ACR...
Pediatric 30 criteria for improvement. In a study of 18 patients with systemic arthritis, an excellent response was found in all patients treated with a combination of intravenous pulse corticosteroids and cyclophosphamide 400 mg/m² given every 3 months with methotrexate 10 mg/m² per week when treated early in the disease course for 1 year.

**Biologic-Modifying Medications**

**Anti–Tumor Necrosis Factor Medications.** Etanercept, a soluble tumor necrosis factor (TNF) receptor, was found to be effective in a 2-phase withdrawal study (Table 5). Etanercept demonstrated sustained benefit in the majority of patients after 2 and 4 years, although methotrexate was added for many of the patients and prednisone in some. These findings were confirmed in the large German etanercept registry. More than 50% of patients have a response greater than the ACR Pediatric 70 level.

Several uncontrolled studies have suggested that etanercept is less effective in patients with systemic arthritis and that the initial response is often not sustained. An excellent response to etanercept and infliximab was found in 2 open studies of 50 patients with juvenile spondyloarthropathy. Higher doses of etanercept do not appear to increase efficacy among the approximately 25% of these children who do not respond to etanercept. No controlled studies were published on the combination of etanercept with methotrexate vs etanercept or methotrexate alone, although in the German registry data there was a higher ACR Pediatric 70 response in patients with systemic arthritis receiving a methotrexate-etanercept combination as opposed to etanercept monotherapy. There are no reports on the radiologic effects of etanercept or other anti-TNF medications in JIA, although marked decreases in the radiologic progression were found in adults with rheumatoid arthritis.

Adverse effects of etanercept are generally mild, mainly injection site

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**Table 6. Efficacy of Common Medication Used to Treat Juvenile Idiopathic Arthritis**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Persistent Oligoarthritis Juvenile Idiopathic Arthritis</th>
<th>Polyarthritis Juvenile Idiopathic Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Mid-moderate</td>
<td>Moderate‡</td>
</tr>
<tr>
<td>Intra-articular corticosteroids</td>
<td>Significant†</td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Unknown</td>
<td>Moderate†</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Unclear</td>
<td>Moderate</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Unknown</td>
<td>Significant</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Unknown</td>
<td>Significant</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Unknown</td>
<td>Significant</td>
</tr>
</tbody>
</table>

Abbreviation: NSAIDs, Nonsteroidal anti-inflammatory drugs.² Non-effective medications (ie, hydroxychloroquine, penicillamine, oral gold, azathioprine) or medications not commonly used (leflunomide, anakinra, cyclophosphamide, intravenous immunoglobulin, thalidomide, colchicine) or not studied in children (ie, minocycline) were not included in this table.

‡There is a lack of evidence on the utility of medications in other types of juvenile idiopathic arthritis.

†For intra-articular corticosteroids efficacy was measured as benefit for more than 6 mo.

‡Significant denotes effective in more than 50% of patients.

§For intra-articular corticosteroids efficacy was measured as benefit for more than 6 mo.

¶Moderate denotes effective in 20% to 50% of patients.
reactions, upper respiratory tract infections, and headaches. However, in a series of 61 patients with polyarthritis and systemic arthritis, 12 (20%) discontinued etanercept due to adverse effects, including neurologic, psychiatric, severe infections, cutaneous vasculitis, and pancytopenia. One case of aseptic meningitis complicating varicella and other bacterial infections needing hospitalization have been reported. One case each of tuberculosis and histoplasmosis were reported in JIA (both to infliximab). No cases of malignancy have been reported in children. Autoimmune phenomena have been reported in several children or young adults with JIA. Several cases of a uveitis flare or the new development of uveitis were reported during use of etanercept. Adult screening guidelines for tuberculosis, at a minimum using purified protein derivative skin testing prior to anti-TNF therapy, are generally adopted in pediatric practice.

Controlled studies of the anti-TNF antibodies infliximab and adalimumab are under way for polyarthritis. Several uncontrolled studies have shown that infliximab has an efficacy similar to etanercept, including young adults with JIA. Patients receiving infliximab often develop adverse reactions during infusion, including anaphylaxis, since infliximab is based on a murine protein. Premedication with acetaminophen, diphenhydramine, and occasionally hydrocortisone usually prevents or minimizes these reactions. The open phase of a large adalimumab trial found a 78% ACR Pediatric 30 response when given at a dose of 24 mg/m² subcutaneously every other week (maximum 40 mg). Patients receiving concurrent methotrexate had a higher response rate than those treated only with adalimumab, although the study power was not adequate to detect a significant difference.

Interleukin 1 Receptor Antagonists. There are no controlled studies of anakinra, an interleukin (IL) 1 receptor antagonist, in JIA. An open 12-week study of 82 patients with a polyarthritis course who were given subcutaneous injections of anakinra at 1 mg/kg per day showed an ACR Pediatric response in 46 (58%) of the patients, less than the open phase of anti-TNF studies. No differences were seen in children with or without concurrent methotrexate. The need for daily injections may also increase the difficulty of giving anakinra.

Initial promising results using anakinra for systemic arthritis have been reported for both the systemic and articular components, including patients not responsive to anti-TNF medications. In the study of polyarthritis, patients with systemic-onset disease showed a more favorable response than those with polyarthritis or oligoarthritis-onset. Sera from patients with systemic arthritis stimulated IL-1 gene expression and production in mononuclear blood cells from healthy individuals, providing rationale for this approach.

Figure 5. Algorithm for Medical Treatment of Polyarthritis in Juvenile Idiopathic Arthritis (JIA)

Patient With Polyarthritis JIA

Rheumatoid Factor Positive

Treat as Adult Rheumatoid Arthritis

Rheumatoid Factor Negative

Nonsteroidal Anti-inflammatory Drug for up to 6 Week Period

Consider Intra-articular Triamcinolone Hexacetonide for Selected Joints

Consider Oral Steroid as Bridging Medication or During Serious Disease Flare

Observe

Continued Improvement or Remission

Disease Flare

Oral Methotrexate 10 mg/m²/wk
Alternatives: Sulfasalazine or Leflunomide
Consider Oral Steroid as Bridging Medication or During Serious Disease Flare

Observe

Parenteral Methotrexate 15 mg/m²/wk
Consider Oral Steroid as Bridging Medication or During Serious Disease Flare

Observe

Parenteral Methotrexate 15 mg/m²/wk
Consider Oral Steroid as Bridging Medication or During Serious Disease Flare

Parenteral Methotrexate 15 mg/m²/wk
Consider Oral Steroid as Bridging Medication or During Serious Disease Flare

For Patients With Systemic Onset JIA, Consider Interleukin 1 Receptor Antagonist
Intravenous Immunoglobulin. Two controlled studies did not find intravenous immunoglobulin (IVIg) to be effective in the treatment of the arthritis component of systemic arthritis and polyarthritis JIA (Table 5). However, both studies had a low power to detect significant differences. There may be more benefit for IVIg in the first year of the disease and for the treatment of the systemic features of systemic arthritis, but this has not been examined in a controlled study.

Type II Collagen. An uncontrolled pilot trial of oral chicken type II collagen in 10 patients with various types of relatively mild JIA showed a significant reduction in active joints in 6 patients.

Other Biologic-Modifying Drugs

An important cytokine in the pathogenesis of systemic arthritis is IL-6. An open series of 11 patients with systemic arthritis given anti–IL-6 receptor antibody intravenously at 8 mg/kg every 2 weeks reported an ACR Pediatric 70 response in 7 of the patients after the second dose.

There are no studies in JIA of new medications found to be effective in rheumatoid arthritis, including rituximab (anti-CD20 B-cell antibodies) or abatacept (anti-CD28, T-cell costimulator antibodies).

There are no studies on the early use of biologic-modifying medications or the effect of early induction therapy including a combination of methotrexate and biologic medications with or without steroid use.

Autologous Stem Cell Transplantation

Wulffraat et al reported on 34 children with longstanding and unresponsive systemic and polyarthritis JIA who underwent autologous stem cell transplantation (ASCT) with nonautoreactive T-cell precursors, with a mean follow-up of 29 months (range, 12-60). Complete drug-free remission was reported in 18 (53%) patients, partial ACR Pediatric 30 response in 6 (18%), and no improvement in 7 (21%). There were 5 (15%) mortalities following ASCT, 3 from early post-ASCT infectious-associated macrophage activation syndrome and 2 non-responsive patients 13 and 16 months following ASCT.

There are still many open issues regarding the ASCT protocol; therefore, ASCT must still be regarded as an experimental procedure for patients with severe and unremitting disease.

Summary of Treatment Evidence for JIA Subtypes

The summary and algorithms are based on our data interpretation. Internationally recognized guidelines have not been adopted in JIA.

Oligoarthritis. Approximately 1/4 to 1/3 of patients will respond to NSAIDs. In patients not responsive to NSAIDs after 4 to 6 weeks, or patients presenting with flexion contractures or leg length discrepancies, intra-articular corticosteroid injections, especially triamcinolone hexace-
Polyarthritis, Rheumatoid Factor Negative. NSAIDs are mostly not effective as disease-modifying medications and should not be used as a sole medication if not effective after a trial of several weeks (Figure 5) (Table 6). The use of an NSAID is more for symptomatic control. Methotrexate should be preferred method of corticosteroid administration, although one controlled study found that patients who received early intravenous methylprednisolone needed fewer total systemic corticosteroids than patients starting corticosteroids orally.

Intra-articular corticosteroid injections, methotrexate, and anti-TNF medications appear to be less beneficial than in other subtypes of JIA, both for the systemic and arthritis components. While IVlg is not effective for the treatment of arthritis, there may be some benefit including a corticosteroid-sparing effect, on the systemic component.

Uncontrolled studies have shown promising results using anti–IL-6 receptor antibodies, anakinra, thalidomide, or early treatment with a combination of cyclophosphamide, methotrexate, and intravenous pulse corticosteroids. For patients with severe, unresponsive systemic or polyarthritis JIA, ASCT may be used as a last resort.

Treatment for the macrophage activation syndrome includes high-dose intravenous corticosteroids and if not rapidly effective, cyclosporine should be added.

Enthesitis-Related Arthritis. There is little evidence-based medicine for this form of JIA. Open series studies have indicated that sulfasalazine may be beneficial, particularly for boys aged 9 years or older with peripheral arthritis, although in the one small controlled study, there was no significant benefit for sulfasalazine. There are no studies of methotrexate use. Open studies found that anti-TNF medications were highly effective.

Psoriatic Arthritis. There are no treatment studies of psoriatic arthritis in children. The presentation of psoriatic arthritis can be as oligoarthritis, polyarthritis and enthesitis-related arthritis and until other evidence is reported should be treated as the parallel JIA subset.

CONCLUSION AND FUTURE DIRECTIONS

The development of new therapies has markedly increased the ability to effectively treat children with JIA and the future appears promising. However, there is still a lack of evidence-based medicine in the treatment of some JIA subtypes. The effect of early aggressive therapy on the disease course, including the potential use of combination induction therapy, has not been studied. The long-term disease-modifying effects of methotrexate and biologic medications on remission rates, radiologic changes, functional capabilities, the prevention of surgery, and the long-term adverse effects are unknown. Future multicenter controlled studies and postmarketing surveillance are necessary to address these issues.

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