Medical Treatment of Juvenile Idiopathic Arthritis

Philip J. Hashkes, MD, MSc
Ronald M. Laxer, MD, FRCPC

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. There is a lack of evidence for the optimal treatment of systemic and enthesitis-related arthritis.

Conclusions Despite many advances in the treatment of JIA, there is still a lack of evidence for treatment of several disease subtypes. The treatment plan needs to be individualized based on the JIA subtype.

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JUVENILE IDIOPATHIC ARTHRITIS (JIA), previously called juvenile rheumatoid arthritis until recent reclassification, is the most common rheumatic disease of childhood.[1] JIA is defined as persistent arthritis for more than 6 weeks with an onset at less than 16 years of age, after excluding other causes. JIA consists of several subtypes (TABLE 1, FIGURE 1).[2,3] Recent data show that most children never achieve a long-term remission, thus the burden of disease to the patient, family, and ultimately society is large.[4-14] It is important to recognize the disease and to treat early, before soft-tissue deformities and joint damage become irreversible (FIGURE 2).

The treatment of JIA combines anti-inflammatory and immunomodulatory medications with physical and occupational therapy, an occasional need for surgery, nutritional support, and psychosocial and educational partnership with patients and parents. The treatment of JIA has changed markedly in the last 15 years, yet many children are not treated by pediatric rheumatologists.[15] This review summarizes the current evidence-based medical therapy for JIA (not including uveitis) and offers a rational approach for the treatment of the various subtypes of disease.

See also Patient Page.

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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 arthritidies of childhood and searched all drugs used to treat inflammatory arthritidies (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-

Author Affiliations: Section of Pediatric Rheumatology, Department of Rheumatic Diseases, Cleveland Clinic Foundation, Cleveland, Ohio (Dr Hashkes); Department of Clinical and Academic Affairs, The Hospital for Sick Children and Department of Pediatrics and Medicine, The University of Toronto, Toronto, Ontario (Dr Laxer).
Corresponding Author: Philip J. Hashkes, MD, MSc, Department of Rheumatic Diseases A50, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (hashkep@ccf.org).

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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.

Table 1. Subtypes of Juvenile Idiopathic Arthritis*

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

*Adapted from Petty et al.[2]

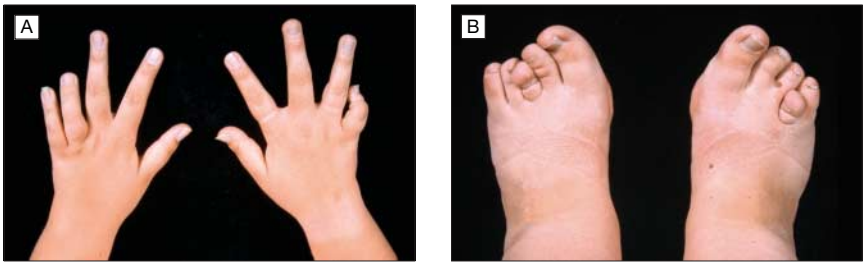
Outcome Measures

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).[49] For older trials, we used the responder measure defined by the authors. There was a large variance in those outcome definitions.

Figure 1. Patients With Oligoarthritis and With Systemic Arthritis

A, Three-year-old girl with oligoarthritis involving the left knee. Swelling, flexion contracture, muscle wasting, and a longer leg on the affected side. B, Patient with systemic arthritis demonstrating characteristic erythematous macular rash on forearm with Koebner phenomena (exacerbation of rash by minor trauma).

Figure 2. Twelve-Year-Old Girl With Polyarthritis



A, Severe growth deformities involving fingers. B, Same patient demonstrating severe growth deformities involving toes.

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.[4,50] Earlier cartilage damage was demonstrated using magnetic resonance imaging.[51]

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.[4-14] Between 30% and 40% of patients have significant long-term disabilities including unemployment, and between 25% and 50% need major surgery, including joint replacement.[6,11-14] Patients with oligoarthritis frequently develop leg length inequality and periarticular muscle atrophy.[52] 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.[4,53-56]

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.[57] Patients with systemic arthritis who are corticosteroid dependent for control of systemic symptoms and have a platelet count of more than $600\times10^3/\mu L$ after 6 months of disease, or who have a G-C macrophage migration inhibitory factor gene polymorphism have a poor outcome.[58,59]

Nonsteroidal Anti-inflammatory Drugs. None of the studies of aspirin or

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Table 2. Controlled Clinical Trials of NSAIDs in Juvenile Idiopathic Arthritis

Source	No. of Patients	Study Type	Length of Treatment, wk	Type of Arthritis	Definition of Response	Daily Medication	Responders, %	Comments
Levinson et al,[16] 1977	107	Randomized, double-blind, multicenter	12	All types	% Improvement in index of active joints	Tolmetin 15-30 mg/kg Aspirin 50-100 mg/kg	25 26	Similar adverse effects
Makela,[17] 1977	18	Randomized, double-blind, crossover	8 for each drug	Not stated	Physician preference for drug	Naproxen 6.5 mg/kg Aspirin 60 mg/kg	46 27	Equal efficacy in 27% of patients
Bhettay and Thomson,[18] 1978	30	Randomized, double-blind, crossover	2 for each drug	All types	Patient preference for drug	Ketoprofen 50 or 100 mg Indomethacin 50 or 100 mg	25 75*	Dose based on weight; no difference in adverse effects
Brewer et al,[19] 1982	99	Randomized, double-blind, multicenter	12	All types	Any improvement in physician global assessment	Fenoprofen 900-1800 mg/m^2 Aspirin 1500-3000 mg/m^2	62 63	Dose increased after 4 wk; more patients discontinued aspirin due to adverse effects
Haapasaari et al,[20] 1983	45	Randomized, double-blind	2	All types	Any improvement in 4-point physician global scale	Diclofenac 2-3 mg/kg Aspirin 50-100 mg/kg Placebo	73* 50* 27	Significantly fewer adverse effects in diclofenac group vs aspirin
Kvien et al,[21] 1984	80	Randomized, double-blind	24	Oligoarthritis, polyarthritis	% Improvement in index of active joints	Naproxen 10 mg/kg Aspirin 75 mg/kg	39 22	More patients discontinued aspirin due to adverse effects
Bhettay,[22] 1986	30	Randomized, double-blind, crossover	3 for each drug	All types	Any improvement in physician global assessment	Sulindac 50, 75, or 150 mg Aspirin 1500, 2700, or 3600 mg	22 25	Dose determined by weight
Williams et al,[23] 1986	47	Randomized, double-blind, multicenter, crossover	4 for each drug	Oligoarthritis, polyarthritis	Physician preference for drug	Naproxen 15 mg/kg Piroxicam 5, 10, 15, or 20 mg	24 26	Dose determined by weight
Garcia-Morteo et al,[24] 1987	26	Randomized, double-blind	12	Polyarthritis	Any improvement in physician global assessment	Naproxen 12.5 mg/kg Piroxicam 5, 10, or 15 mg	38 67*	No significant differences by patient-parent assessment; dose determined by weight
Leak et al,[25] 1988	28	Randomized, single-blind, crossover	4 for each drug	Oligoarthritis, polyarthritis	No change or any improvement in physician global assessment	Naproxen 10 mg/kg Diclofenac 2 mg/kg Tolmetin 25 mg/kg	89 89 86	
Giannini et al,[26] 1990	92	Randomized, double-blind, multicenter	12	All types	Any improvement in physician global assessment	Ibuprofen 30-40 mg/kg Aspirin 60-80 mg/kg	79 77	More adverse effects in aspirin group
Kiss et al,[27] 2003 (abstract)	310	Randomized, double-blind, international, non-inferiority	12	Oligoarthritis, polyarthritis	ACR Pediatric 30	Rofecoxib 0.3 mg/kg (maximum 12.5 mg) Rofecoxib 0.6 mg/kg (maximum 25 mg) Naproxen 15 mg/kg	46 54 55	Only low dose rofecoxib group had significantly less gastrointestinal adverse effects
Gedalia et al,[28] 2004 (abstract)	209	Randomized, double-blind, international, non-inferiority	12	Oligoarthritis, polyarthritis	ACR Pediatric 30	Naproxen 5-7.5 mg/kg† Meloxicam 0.125-0.25 mg/kg Meloxicam 0.25-0.375 mg/kg	4 wk 42 12 wk 69 4 wk 47 12 wk 74 4 wk 48 12 wk 68‡	Dose increased after 4 wk
Ruperto et al,[29] 2005	225	Randomized, double-blind, international, non-inferiority	52	Oligoarthritis, polyarthritis	ACR Pediatric 30	Naproxen 10 mg/kg† Meloxicam 0.125 mg Meloxicam 0.25 mg	74 77 76	

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

Source	Patient No.	Study Type	Length of Treatment, wk	Type of Arthritis	Definition of Response	Medication	Responders, %	Comments
Kvien et al,[30] 1985	77	Randomized, open	50	Oligoarthritis, polyarthritis	50% Improvement in physician global assessment	Intramuscular gold 0.7 mg/kg/injection D-penicillamine 10 mg/kg per d	59 50	
Kvien et al,[31] 1985	72	Randomized, open	50	Oligoarthritis, polyarthritis	50% Improvement in physician global assessment	Hydroxychloroquine 5 mg/kg per d Intramuscular gold 0.7 mg/kg per injection D-penicillamine 10 mg/kg per d	71 67 67	
Prieur et al,[32] 1985	74	Randomized, double-blind, multicenter	26	Oligoarthritis, polyarthritis	Any improvement in physician global assessment	D-penicillamine 5 and after 2 mo 10 mg/kg per d Placebo	55* 28	
Brewer, et al,[33] 1986	162	Randomized, double-blind, international	52	Polyarthritis	Composite index†	Hydroxychloroquine 6 mg/kg/d D-penicillamine 10 mg/kg/d Placebo	30 42 32	
Kvien et al,[34] 1986	32	Randomized, double-blind	16	All types	25% Improvement in index of active joints	Azathioprine 2-2.5 mg/kg per d Placebo	41 27	
Giannini et al,[35] 1990	231	Randomized, double-blind, international	26	All types, >3 active joints	Composite index†	Oral gold 0.15-0.2 mg/kg per d Placebo	34 46	
Hoza et al,[36] 1991	39	Randomized, double-blind	26	Oligoarthritis, polyarthritis	Any improvement in 4 criteria: active joints, pain, morning stiffness, erythrocyte sedimentation rate, functional capacity	Sulfasalazine 20-30 mg/kg/d Chloroquine 3-4 mg/kg per d	48 28	More adverse reactions with sulfasalazine
Giannini et al,[37] 1992	127	Randomized, double-blind, international	26	All types, ≥3 active joints	Composite index†	Oral methotrexate 5 mg/m^2 body surface area per wk Oral methotrexate 10 mg/m^2 body surface area per wk Placebo	32 65* 36	Significant effect only of methotrexate 10 mg/m^2
Picco et al,[38] 1996	22	Randomized, open	26	Systemic	Decrease in daily oral corticosteroid dose at 6 mos	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 Oral 1 mg/kg per d	74* 34	Significant less cumulative dose in initial intraveneous group
Van Rossum et al,[39] 1998	69	Randomized, double-blind, multicenter	24	Oligoarthritis, polyarthritis	Pediatric ACR 30§	Sulfasalazine 50 mg/kg/d, maximum 2 g per d Placebo	44* 21	More sulfasalazine adverse effects
Woo et al,[40] 2000	88	Randomized, double-blind, crossover, multicenter	16	Systemic or oligoarthritis with polyarthritis course	ACR Pediatric 30§	Oral methotrexate 15-20 mg/m^2 per wk Placebo	Systemic 25 Oligoarthritis 48* Systemic 16 Oligoarthritis 18	Methotrexate dose allowed to increase after 2 mo
Burgos-Vargas et al,[110] 2002	33	Randomized, double-blind	26	Enthesitis-related	Reduction in active joints	Sulfasalazine 30-60 mg/kg per d, maximum 2000 mg per d Placebo	46 42	Significantly more improvement in sulfasalizine group by physician and patient assessment
Ruperto et al,[41] 2004	80‡	Randomized, open, international	26	Polyarthritis course	ACR Pediatric 30	Parenteral methotrexate 15 mg/m^2 per wk Parenteral methotrexate 30 mg/m^2 per wk	63 58	
Silverman et al,[42] 2005	94	Randomized, double-blind, multi-center	16	Polyarthritis course	Pediatric ACR 30	Leflunomide 10 mg every other day to 20 mg per d Methotrexate 0.5 mg/kg per wk	68 89*	Leflunomide dose per weight; methotrexate maximum dose 25 mg/wk

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/m^2/week (out of 595).
§Without functional measure.

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

Source	No. of Patients	Study Type	Length of Follow-up	Type of Arthritis	Definition of Response	Medication	Responders, %		Comments
Balogh and Ruzsonyi,[43] 1987	23	Randomized, double-blind	6 wk	Oligoarthritis	Difference in knee circumference	Triamcinolone hexacetonide†	−1.7 cm*		Only knees studied
						Betamethasone†	+1.0 cm		
Zulian et al,[44] 2003	85 (130 joints)	Randomized, blinded assessment	24 mo	Oligoarthritis	≥60% decrease in articular score	Triamcinolone hexacetonide 1 mg/kg-40 mg	6 mo	81*	Dose depended on joint size
							12 mo	67*	
							24 mo	60*	
						Triamcinolone acetonide 1 mg/kg-40 mg	6 mo	53	
							12 mo	43	
							24 mo	33	
Zulian et al,[45] 2004	37 (43 paired joints with inflammation)	Randomized, double-blind	24 mo	Oligoarthritis, polyarthritis	% Joints without inflammation	Triamcinolone hexacetonide 1 mg/kg-40 mg	6 mo	90*	
							12 mo	85*	
							24 mo	77*	
						Triamcinolone acetonide 2 mg/kg-80 mg	6 mo	62	
							12 mo	49	
							24 mo	39	

*Significant positive effect.
†Dose not stated.

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

Source	No. of Patients	Study Type	Length of Treatment, wk	Type of Arthritis	Definition of Response	Medication	Responders/ Flare, %	Comments
Silverman et al,[46] 1994	31	Randomized, double-blind, multicenter	26	Systemic	Physician global assessment	Intravenous immunoglobulin 1.5 g/kg per mo	50	In first 2 mo drug was given biweekly; small study power
						Placebo	27	
Giannini et al,[47] 1996	19§	Randomized, double-blind, withdrawal, multicenter	16	Polyarthritis	Composite index‡	Intravenous immunoglobulin 2 g/kg per mo	20‖	Small study power
						Placebo	80‖	
Lovell et al,[48] 2000	51†	Randomized, double-blind, withdrawal, multicenter	16	Polyarthritis-course	Modified ACR Pediatric 30 for flare	Subcutaneous etanercept 0.4 mg/kg per dose twice weekly	28‖*	
						Placebo	81‖	

Abbreviations: ACR, American College of Rheumatology.
*Significant positive effect.
†51 responders in 3-month open phase were randomized from 69 patients.
‡Composite index: ≥25% reduction in active joints and improvement in physician and patient global assessment.
§19 responders in 2-month open phase were randomized from 25 patients.
‖Percent of patients who experienced arthritis flares.

other NSAIDs were placebo controlled, since it is ethically difficult to perform placebo controlled studies in children, particularly for drugs benefiting adults (Table 2).[60] In a summary of studies, only about 25% to 33% of the patients, mainly those with oligoarthritis, showed a significant response to NSAIDs.[61] A 4- to 6-week trial of an individual NSAID is necessary to assess its efficacy.[62] 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.[19-21,26]

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%.

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

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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).[16,17,21,25-27] 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).[18-20,22-25,28,29] Comparative efficacy of nabumetone was reported in an open study.[63]

Serious gastrointestinal adverse effects are rare,[64,65] although as many as 28% of children develop gastrointestinal symptoms.[66] Of these, 34% to 75% were found to have gastritis and/or duodenitis.[66,67] Another important adverse effect is the development of pseudoporphyria, most often associated with naproxen use in whites with fair hair.[68,69] Central nervous system adverse effects may occur including headaches and disorientation, especially from indomethacin. Renal adverse effects, particularly papillary necrosis or tubular function abnormalities, are uncommon but are more frequent during concurrent use of more than 1 NSAID.[70,71] Cardiovascular adverse effects were not 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.[29,64]

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.[72] 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.[73] One controlled study showed that the use of intravenous minipulses 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).[38]

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.[43-45,74-80] Radiographic and magnetic resonance imaging studies have shown a marked decrease in synovial volume after injection without deleterious effects on the cartilage.[75] 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.[52] The efficacy is less in other JIA subtypes, especially systemic arthritis patients with the G-C macrophage migration inhibitory factor gene polymorphism.[59,76,77]

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.[74] Repeated injections to an individual joint were not found to be associated with joint or cartilage damage.[81] Asymptomatic calcifications are occasionally found after injections. In one series examining the outcome of hip injections, aseptic necrosis did not occur.[78] The long-acting triamcinolone hexacetonide is more effective and has a longer effect than other forms of injectable corticosteroids (Table 4).[43-45] Younger children or children needing multiple joint injections usually require sedation.

Methotrexate. Methotrexate is the treatment cornerstone for most patients with polyarthritis (Table 3).[37,82] An open randomized study showed that increasing the dose of methotrexate to 15 mg/m^2 per week and giving methotrexate parenterally was effective for most patients not responsive to 10 mg/m^2 per week. There was no additional advantage in giving higher doses up to 30 mg/m^2 per week.[41]

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.[40,83-85] Methotrexate may exhibit a disease-modifying effect as the radiologic damage progression rate was decreased in 2 small uncontrolled series.[86,87]

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.[88-90] One study found that continuing methotrexate for more than 1 year of inactive disease was associated with a lower rate of flare,[88] while another did not find differences between patients who discontinued methotrexate 3 months after disease inactivity vs 1

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year.[89] The level of myeloid-basic protein 14 when methotrexate was discontinued was a better predictor of flare.[89] Nearly 90% of patients respond when methotrexate is restarted.[88,90]

Since food decreases the bioavailability of methotrexate, it is advised to give methotrexate on an empty stomach.[91] At doses of 10 mg/m^2 per week, there is no difference in the efficacy of methotrexate whether administered orally or parenterally, although parenteral methotrexate may be better tolerated.[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^2.[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.[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.[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^2 per week detected significant hematologic and liver enzyme abnormalities as often as testing at monthly intervals.[98] While mild elevations of liver enzymes occur frequently, no cases of severe, irreversible liver fibrosis have been reported in JIA.[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.[101] Pulmonary toxicity is very rare in children and pulmonary function was normal in patients with JIA on long-term methotrexate.[102,103] Nodulosis has rarely been reported.[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.[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.[30-33,35,110-112] One study did not find parenteral gold to be more effective than D-penicillamine or hydroxycholoquine.[31]

Most studies of sulfasalazine were not controlled.[113] One controlled study showed that sulfasalazine is effective in the treatment of oligoarthritis and polyarthritis.[39] However, in a small placebo-controlled study of juvenile spondyloarthropathy,[114] and a study comparing sulfasalazine with chloroquine in oligoarthritis and polyarthritis,[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[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.[39,113] Adverse effects may be especially severe in patients with systemic arthritis.[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.[42] Most of the patients responsive to leflunomide maintained their response in a 2-year open label extension study.[115] No significant differences in adverse effects were found. A controlled study of azathioprine did not find a significantly greater efficacy than placebo.[34] There are no studies of minocycline 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.[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.[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.[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.[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

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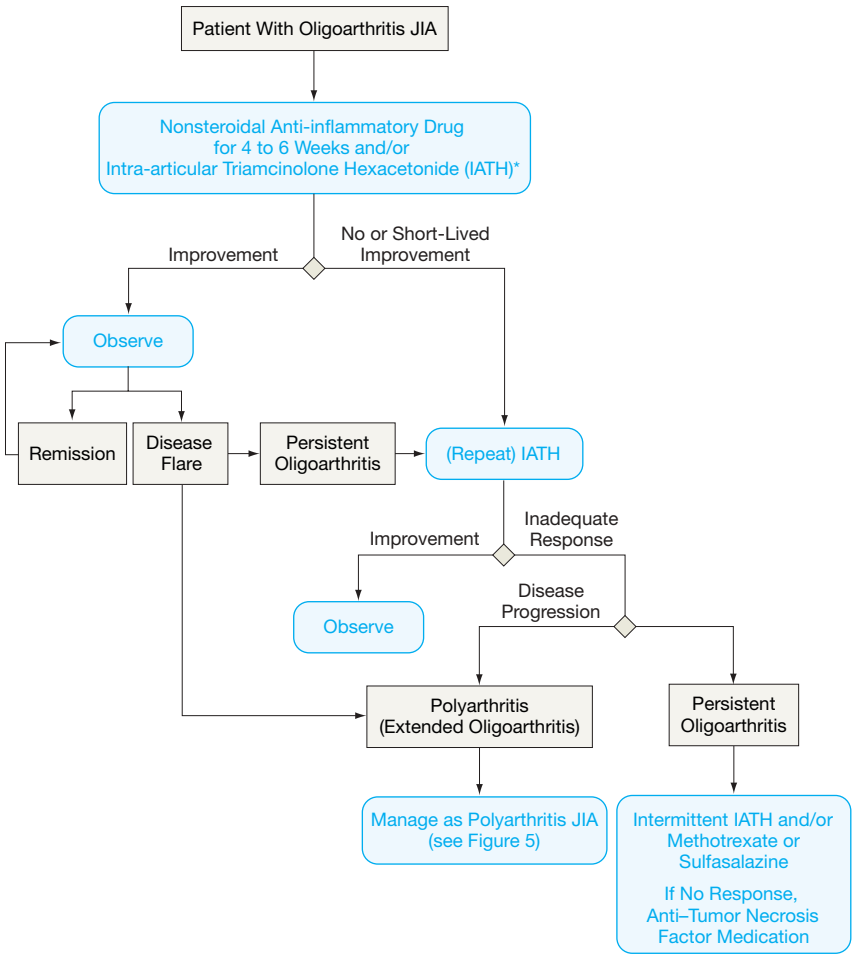
Figure 4. Algorithm for Medical Treatment of Oligoarthritis in Juvenile Idiopathic Arthritis (JIA)



*Prefer early intra-articular triamcinolone hexacetonide if patient has local complications: contractures, leg length discrepancy, significant muscle atrophy.

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

Medication	Efficacy: Persistent Oligoarthritis Juvenile Idiopathic Arthritis	Efficacy: Polyarthritis Juvenile Idiopathic Arthritis
NSAIDs	Mild-moderate	Mild‡
Intra-articular corticosteroids§	Significant‖	Moderate¶
Methotrexate	Unknown	Significant
Sulfasalazine	Unclear	Moderate
Etanercept	Unknown	Significant
Infliximab	Unknown	Significant
Adalimumab	Unknown	Significant

Abbreviation: NSAIDs, Nonsteroidal anti-inflammatory drugs.
*Non-effective medications (ie, hydroxychloroquine penicillamine, oral gold, azathioprine) or medications not commonly used (leflunomide, anakinra, cyclophosphamide, intravenous immunoglobulin, thalidomide, collagen) 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.
‡Mild denotes effective in up to 25% of patients.
§For intra-articular steroids efficacy was measured as benefit for more than 6 mo.
‖Significant denotes effective in more than 50% of patients.
¶Moderate denotes effective in 25% to 50% of patients.

Pediatric 30 criteria for improvement.[122] 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/m^2 given every 3 months with methotrexate 10 mg/m^2 per week when treated early in the disease course for 1 year.[123]

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).[48] 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.[124,125] These findings were confirmed in the large German etanercept registry.[126] More than 50% of patients have a response greater than the ACR Pediatric 70 level.[124-126]

Several uncontrolled studies have suggested that etanercept is less effective in patients with systemic arthritis and that the initial response is often not sustained.[48,127-130] An excellent response to etanercept and infliximab was found in 2 open studies of 50 patients with juvenile spondyloarthropathy.[131,132] Higher doses of etanercept do not appear to increase efficacy among the approximately 25% of these children who do not respond to etanercept.[133] 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.[134] 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.[135]

Adverse effects of etanercept are generally mild, mainly injection site

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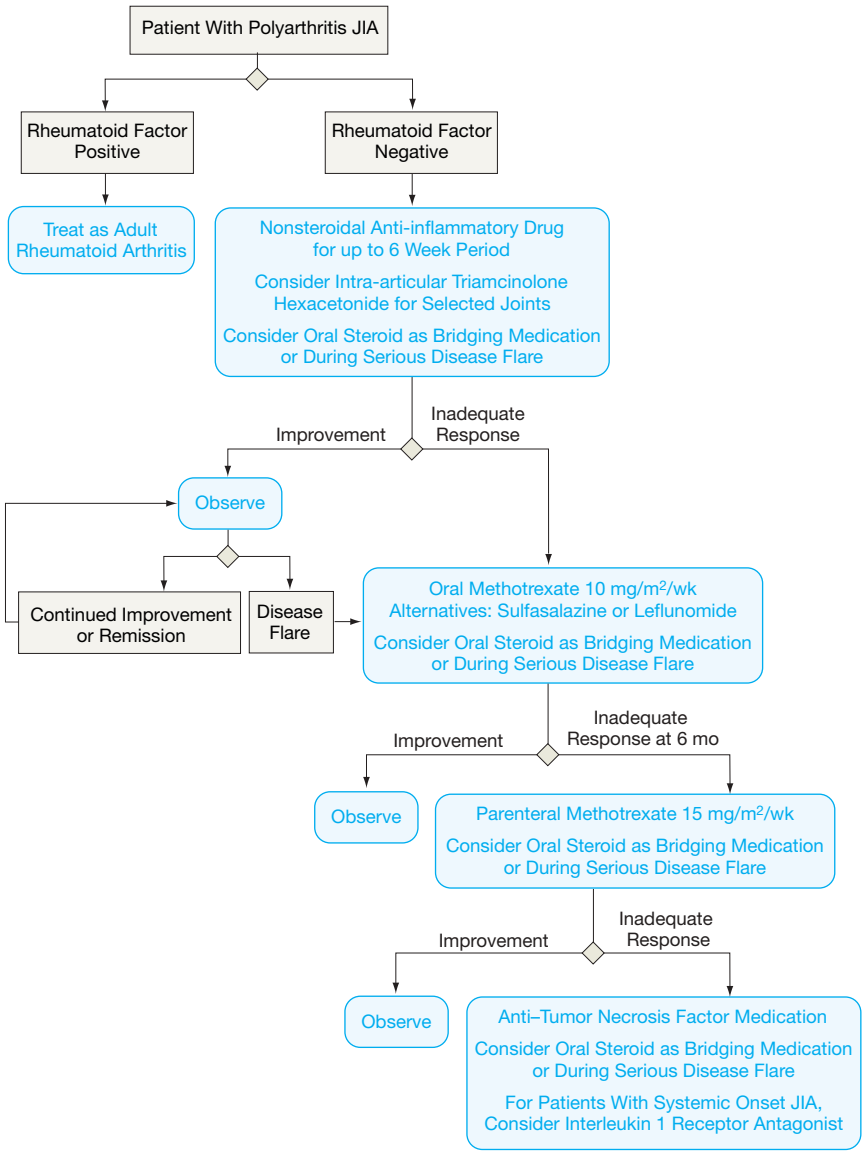
reactions, upper respiratory tract infections, and headaches. However, in a series of 61 patients with polyarthritis and systemic arthritis, 12 (20%) discontinued etanercept due to adverse effects, including neurologic, psychiatric, severe infections, cutaneous vasculitis, and pancytopenia.[128] One case of aseptic meningitis-complicating varicella and other bacterial infections needing hospitalization have been reported.[48,124-128] One case each of tuberculosis and histoplasmosis were reported in JIA (both to infliximab).[136,137] No cases of malignancy have been reported in children. Autoimmune phenomena have been reported in several children or young adults with JIA.[126,138-141] Several cases of a uveitis flare or the new development of uveitis were reported during use of etanercept.[126,128,142] 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.[143-147] Patients receiving infliximab often develop adverse reactions during infusion, including anaphylaxis, since infliximab is based on a murine protein.[148] 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/m^2 subcutaneously every other week (maximum 40 mg).[149] 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 30 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.[150]

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.[151] In the study of polyarthritis, patients with systemic-onset disease showed a more favorable response than those with polyarthritis or oligoarthritis-onset.[150] 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.[152]

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



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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).[46,47] 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,[46,153] 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.[154]

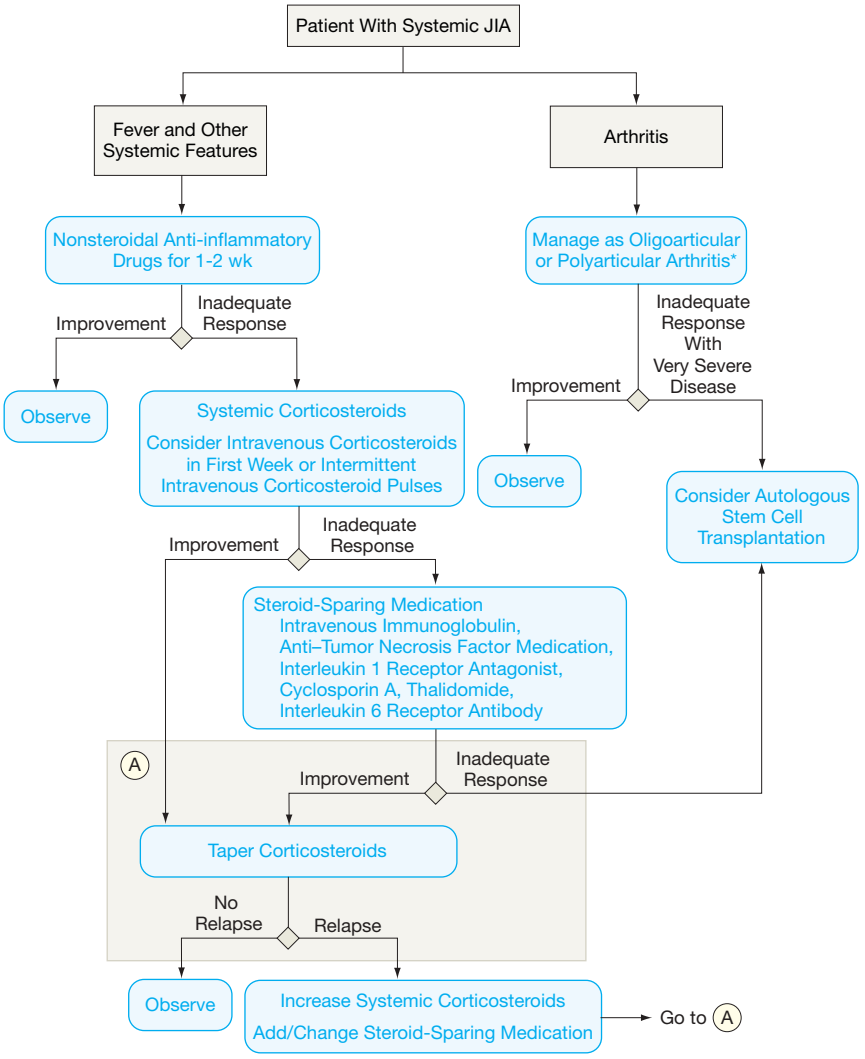
Other Biologic-Modifying Drugs

An important cytokine in the pathogenesis of systemic arthritis is IL-6.[155,156] 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.[157]

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.

Figure 6. Algorithm for Medical Treatment of Systemic Arthritis in Juvenile Idiopathic Arthritis (JIA)



*Methotrexate, intra-articular corticosteroids, antitumor necrosis factor drugs are less effective in systemic arthritis.

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).[158,159] 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 nonresponsive 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 ¼ to ⅓ of patients will respond to NSAIDs (FIGURE 4) (TABLE 6). 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-

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tonide, is effective for most. Patients not responsive to corticosteroid injections or with extended oligoarthritis or small joint involvement should be treated as patients with polyarthritis.

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 symptom control. Methotrexate should be started early, initially at 10 mg/m^2 per week, and if not effective, increased to 15 mg/m^2 per week and given parenterally. Alternatives include the use of sulfasalazine and leflunomide. If not effective, anti-TNF medications should be used, although there is still no evidence whether a combination of methotrexate and anti-TNF medications are more effective than only anti-TNF medications.

Intra-articular corticosteroid injections can be used as an adjunct for 1 or a few painful or swollen joints. Systemic corticosteroids may be necessary as a bridging medication or during flares.

Polyarthritis, Rheumatoid Factor Positive. These patients have a poor outcome and should be treated aggressively per algorithms for rheumatoid arthritis in adults, including the early use of methotrexate and addition of anti-TNF medications in patients with an inadequate response to methotrexate. Although not studied in children, other medications and combination therapy effective in rheumatoid arthritis may be effective.

Systemic Arthritis. There is a particular lack of treatment evidence for systemic arthritis (FIGURE 6). NSAIDs and systemic corticosteroids are often needed for symptomatic (fever, serositis) relief. There is no evidence on the 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 IVIg 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 used be as a last resort.

Treatment for the macrophage activation syndrome includes high-dose intravenous corticosteroid pulses 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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