Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Brewer, Giannini, Kuzmina, et al., 1986 **#1181** **AND** **Van Kerchove, Giannini, and Lovell, 1988** **#1120**	**Geographical location:** US (13 centers; N = 65 patients); Soviet Union (5 centers; N = 97 patients) **Study dates:** NR **Funding source:** NIH Grant from Winthrop laboratories and funds from Merck Sharp Dohm Laboratories **Setting:** 18 pediatric rheumatology centers **Study design:** RCT **Intervention(s):** - DMARD name: PCN - Dose: 5 mg/kg/day - Titration: Increased at 2 months to 10 mg/kg/day - N = 54 - DMARD name: HCQ - Dose: 3 mg/kg/day - Titration: Increased at 2 months to 6mg/kg/day - N = 57 **Comparator(s):** Placebo (N = 51) **Were additional arthritis medications allowed?:** Yes: NSAIDs, antibiotics,	**Number of patients:** N = 162 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NR - Began treatment: 162 - Completed treatment: 6 months = 143 (88%) 12 months = 123 (76%) - Withdrawals/losses to followup: NR **Age:** - Range: 18 months – 17 years - Mean 9.7 years **Sex:** - Female: 122 (75.3%) - Male: 40 (24.7%) **Race/ethnicity:** NR **JIA diagnosis:** JRA Polyarticular 142, pauciarticular 11, systemic 9 **Baseline severity:** Active joint count: PCN: 18 ± 13.5 HCQ: 18.6 ± 13.1 Placebo: 16.3 ± 10.6 Duration of disease: Mean 3.2 years ESR: PCN: 32 ± 23	**1) Active joint count:** Degree of change at 6 months: *Drug* | *Mean* | *Median* | *95% CI* PCN | -3.0 | -3 | -4.8 to -1.1 HCQ | -2.8 | -2 | -5 to - 0.7 PLA | -2.9 | -1.5 | -5.6 to 0.2 Degree of change at 12 months: *Drug* | *Mean* | *Median* | *95% CI* PCN | -3.7 | -3.5 | -5.6 to -1.9 HCQ | -6.7 | -4 | -9.4 to -4 PLA | -5.4 | -4.5 | -8 to -2.8 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** Degree of change at 6 months: *Drug* | *Mean* | *Median* | *95% CI* PCN | -2.5 | -1 | -4.3 to -0.8 HCQ | -0.7 | -1 | -2.3 to 1 PLA | -3.8 | -2 | -6.2 to -1.3 Degree of change at 12 months: *Drug* | *Mean* | *Median* | *95% CI* PCN | -1.4 | -0.5 | -2.9 to -0.04 HCQ | -1.9 | -2 | -4.4 to 0.5 PLA | -3.4 | -3 | -5.8 to -0.9 **4) Global assessment of current status:** By physician: Number (%) much better / better / same / worse / much worse / NA 6 months:	**General comments:** Older medications, PCN not used any longer **Quality assessment:** *Primary outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Fair - Comments: Listed by drug **Applicability:** Good

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	acetaminophen and codeine NSAIDs given per protocol – had to be steady dose, unchanged during study **Study duration:** 12 months **Primary outcome(s):** NR **Secondary outcome(s):** NR	HCQ: 28 ± 23 Placebo: 30 ± 21 **Percentage with uveitis:** NR **Inclusion criteria:** - Met the criteria for JRA established by the American Rheumatism Association or the criteria used in the Soviet Union and Eastern Europe - Presence of severe, clinically active. poorly controlled disease. - Age ≥18 months and ≤ 17 years **Exclusion criteria:** - Clinically important cardiac disorder or other severe or chronic disease - Pregnant or nursing women - Patients scheduled for surgery	PCN: 4(8) / 24(47) / 18(35) / 5(10) / 0 / 0 HCQ: 3(6) / 25(50) / 16(32) / 5(10) / 0 / 1(2) PLA: 6(14) / 15(36) / 17(41) / 2(5) / 1(2) / 1(2) 12 months: PCN: 9(21) / 15(35) / 12 (28) / 7(16) / 0 HCQ: 11(24) / 22(48) / 12(26) / 1(2) / 0 PLA: 7(21) / 11(32) / 14(41) / 2(6)0 By patient/parent: NR **5) Laboratory measures of inflammation:** ESR: Mean decrease (median) 12 months: PCN: 9.4 (4) HCQ: 10 (4) PLA: 10 (4) **6) Discontinuation of DMARD due to:** Remission of disease: NR Inefficacy (n [%]): PCN: 4(36) HCQ: 5(45) PLA: 4(24) Intolerance/AEs (n [%]): PCN: 2(18) HCQ: 3(27) PLA: 3(18) **7) Mortality:** NR **8) Adverse events reported?:** Yes - leucopenia, anemia **9) Other - Total sum of severity:** Degree of change at 6 months:	

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<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
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<tr><th>Drug</th><th>Mean</th><th>Median</th><th>95% CI</th></tr>
<tr><td>PCN</td><td>-23.5</td><td>-15</td><td>-34.7 to -12.3</td></tr>
<tr><td>HCQ</td><td>-15.4</td><td>-10</td><td>-23.9 to - 6.8</td></tr>
<tr><td>PLA</td><td>-12.7</td><td>-12.5</td><td>-24.8 to -0.6</td></tr>
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<tr><td>PLA</td><td>-18.1</td><td>-16</td><td>-24.4 to -11.8</td></tr>
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<tr><td>Giannini, Brewer, Kuzmina, et al., 1992

#1008</td><td>Geographical location: 18 centers in the US and 5 in the Soviet Union

Study dates: NR

Funding source: FDA, NIH, National Arthritis Foundation, Children’s Hospital Research Foundation, Lederle Laboratories

Setting: Specialty centers

Study design: RCT

Intervention(s):
- DMARD name: Methotrexate
- Dose: Very low dose (5 mg/m^2/week) or low dose (10 mg/m^2/week) up to 15 mg/week max
- N: Planned for 30/group

Comparator(s): Placebo</td><td>Number of patients:
- Screened for inclusion: NR
- Eligible for inclusion: NR
- Randomized: 127
- Began treatment: 127
- Completed treatment: 114 (for efficacy analysis); 108 completed the entire 6-month trial
- Withdrawals/losses to followup: 19 discontinued therapy (see under “Results” for details); no reported loss to follow-up

Age:
- Mean (SD): 10.1 years
- Median: NR
- Range: 2.5 to 17.8 years

Sex:
- Female: 96 (76%)
- Male: 31 (24%)

Race/ethnicity: NR</td><td>1) Active joint count:
Very low dose: -5.2
Low dose: -7.2
Placebo: -5.2
p > 0.3

2) Quality of life/functional status:
Composite index:
Very low dose: 32% improved
Low dose: 63%
Placebo: 36%

3) Number of joints with limited range of motion:
Very low dose: -0.5
Low dose: -5.4
Placebo: -0.7
p = 0.04

4) Global assessment of current status:
By physician:
Low dose improved over placebo (p = 0.02)
Very low dose not improved over placebo (p = 0.06)</td><td>General comments: None

Quality assessment:
Primary efficacy outcome:
- Overall rating: Good
- Comments: Well-conducted RCT

Adverse events:
- Overall rating: Good
- Comments: Thorough explanation

Applicability: Good</td></tr>
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Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		JIA diagnosis: JRA		
	Were additional arthritis medications allowed?: Yes: NSAIDs or prednisone Dose of these drugs had to be constant for at least 1 month before randomization and could not be changed **Study duration:** 6 months **Primary outcome(s):** - Physician's global assessment of the patient's response - Articular-severity score - Composite index **Secondary outcome(s):** - Number of joints with swelling - Pain on motion - Tenderness - Limitation of motion - Severity of condition - Duration of morning stiffness - Laboratory changes (hemogram and ESR)	**Baseline severity:** Active joint count (n [SE]): Very low dose: 27 (2) Low dose: 21 (2) Placebo: 24 (2) Duration of disease: Mean 5.1 years Other (specify): Systemic in 32 (25%) **Percentage with uveitis:** NR **Inclusion criteria:** - Criteria for JRA of the ACR or the Soviet Union and Eastern Europe - 3 joints with active arthritis not adequately controlled by NSAIDs or second line agents - At least 18 months and less than 18 years of age **Exclusion criteria:** - Other clinically important severe or chronic disease - Girls who might become pregnant - Receipt of penicillamine, hydroxychloroquine, oral or parenteral gold, or intraarticular or long-acting parenteral steroids within 3 months before randomization - Previous receipt of methotrexate	By patient/parent: NR – results "nearly identical with those of the physician's" **5) Laboratory measures of inflammation:** ESR: Very low dose: 7/28 with an elevated level had a normal value by the final visit Low dose: 13/28 with an elevated level had a normal value by the final visit Placebo: 8/27 with an elevated level had a normal value by the final visit **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** Remission of disease: NR Other reasons: Very low dose: 2 ineffectiveness of drug, 1 AE, 2 intercurrent illness Low dose: 2 AEs, 2 intercurrent illness, 2 "administrative," 1 noncompliance Placebo: 5 ineffectiveness of drug, 1 intercurrent illness, 1 "administrative" reasons **11) Mortality:** None **12) Adverse events reported?:** Yes 8/40 with very low dose: 4 GI problems, 2 headache or dizziness, 2 inflammation of	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			oral mucosa with headache and GI problems 6/47 with low dose: 3 GI problems, 1 ulceration of mucous membranes, 1 headache, 1 headache and abdominal problems 5/41 placebo: All GI problems 15 in very low dose, 15 in low dose, and 5 in placebo had abnormal lab results "judged to be clinically important" – most frequent were alterations in WBC differential, hematuria, and pyuria. Increased aminotransferase levels and anemia were most common with placebo.	
Giannini, Lovell, Silverman, et al., 1996 **#877**	**Geographical location:** 7 centers in US and Canada **Study dates:** Nov 1991-Nov 1994 **Funding source:** FDA, NIH, Immuno AG, Children's Hospital Research Foundation of Cincinnati, Schmidlapp Founation, IRCSS (Italian Research Hospital) **Setting:** Specialty **Study design:** RCT, blinded, with a run-in period between 3 and 6 months. RCT lasted 4 months and had an "escape" provision for those whose symptoms worsened. **Intervention(s):** - DMARD name: IVIG - Dose: 1.5-2.0 g/kg/infusion (100	**Number of patients:** N = 25 in the run-in phase, 19 in the blinded RCT - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 19 - Began treatment: 19 - Completed treatment: 12 completed, 6 "early escape" - Withdrawals/losses to followup: 1 **Age:** - Mean (SD): 10.9 (5.8) (n = 25 in the run-in period) - Median: NR - Range: 2 to 23 years **Sex:** - Female: 22 (88%) - Male: 3 (12%) **Race/ethnicity:** NR **JIA diagnosis:**	**1) Active joint count:** In the RCT, -3% in IVIG group (n = 10), 30% increase in the placebo group (n = 9) **2) Quality of life/functional status:** 19/25 had "clinically important improvement" in the open label and entered the RCT During the RCT, 2/10 in the treatment group "escaped" to higher dosing based on clinically significant worsening. 5/9 in the placebo group escaped to treatment because of clinically significant worsening. **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** By physician: In the RCT, -3% in physician global assessment in the IVIG group (n = 10), 91% increase in global assessment in the placebo group (n = 9)	**General comments:** Includes only subjects who responded to IVIG from the open-label trial – evaluates effectiveness based on lack of "escape" **Quality assessment:** *Primary outcome:* - Overall rating: Fair - Comments: No statistical inference testing; conflict of interest with funding source; main outcome not validated *Adverse events:* - Overall rating: Fair - Comments: No validated AE measure; potential conflict of interest with funding source **Applicability:** Includes only subjects who responded to IVIG from the open-label study

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	g maximum) bimonthly - Titration: After 6 infusions, dose could be increased up to the maximum - N: 25 **Comparator(s):** Placebo **Were additional arthritis medications allowed?:** Yes - NSAIDs, "slow acting antirheumatic drugs (methotrexate, sulfasalazine, hyroxychloroquine), low dose prednisone (< 10 mg/day) **If Yes to above, was this done per protocol or at the discretion of study investigators:** NR **Study duration:** Run-in: 3 to 6 months RCT: 4 months **Primary outcome(s):** - "Clinically important benefit," defined as ≥ 25% improvement in at least 2 of the following: (a) total number of joints with active arthritis, (b) overall articular severity score, (c) physician's global assessment of overall disease activity - "Clinical important worsening," defined as ≥ 25% worse in 2/3 above **Secondary outcome(s):** Juvenile Arthritis Functional	All with poly-JRA Group A: Late onset (> 10 years) but short duration (< 3 years) Group B: ≥ 5 joints with active arthritis, disease before 8 years, short duration (< 3 years) Group C: Longer duration (> 5 years, substantial involvement (≥ 10 joints) **Baseline severity:** Active joint count: 26.7 (± 13.2) at run-in Duration of disease: 4.4 years (± 4.5) at run-in Other (specify): Overall articular severity score: 103 (± 60) Physician global assessment: 5.7 (± 2.0) JAFAR: 11.1 (± 6.5) Elevated ESR: 11/23 **Percentage with uveitis:** NR **Inclusion criteria:** Poly-JRA Between 2 and 23 years **Exclusion criteria:** - Known hypersensitivity to immunoglobulin - Leukopenia (WBC < 1500/mm^3) - Thrombocytopenia (platelets < 100,000/mm^3) - Significant renal or hepatic disease - IgA deficiency - Malignancy	By patient/parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR **11) Mortality:** None **12) Adverse events reported?:** Yes – not broken down by treatment group In the open-label period, 3 patients, and in the RCT, 1 patient experienced AEs associated with the infusion process, namely headache, dizziness, nausea, vomiting, diarrhea, tachycardia, fatigue, and chills. AEs not associated with infusion: In the open-label period, 1 with joint pain, 1 with flare and worsening chronic iritis that required steroids, 1 with fever to 39.9 degrees C related to probable intercurrent illness **13) Other:** Mean time to failure during the RCT in the placebo group was 2.5 months (range 1.8 to	

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	Assessment Report (JAFAR)	- Chronic infection - Immunized with a live virus in past 2 weeks - Pregnancy	3.2 months) In the RCT, 10% increase in JAFAR in the IVIG group (n = 8), 59% increase in the placebo group (n = 7) – sample size smaller because subjects with JAFAR = 0 at baseline were excluded	
Hoza, Kadlecova, Nemcova, et al., 1991 **#1048**	**Geographical location:** Prague, Czechoslovakia **Study dates:** NR **Funding source:** NR **Setting:** Hospital **Study design:** RCT **Intervention(s):** - DMARD name: Sulfasalazine (SSZ) - Dose: 20-30 mg/kg/day - N: 21 **Comparator(s):** - DMARD name: Chloroquin (DLG) - Dose: 3 to 4 mg/kg/day - N: 18 **Were additional arthritis medications allowed?:** Yes: NSAIDs, prednisone NR whether these were added per protocol or at the discretion of clinician/investigator **Study duration:** 6 months	**Number of patients:** N = 39 - Screened for inclusion: - Eligible for inclusion: 39 - Randomized: SSZ, 21; DLG, 18 - Began treatment: 39 - Completed treatment: 34 - Withdrawals/losses to followup: 5 withdrawals **Age:** NR **Sex:** - Female: 26 (66.7%) - Male: 13 (33.3%) **Race/ethnicity:** NR **JIA diagnosis:** *SSZ:* Poly: 11 Oligo: 8 Systemic: 2 *DLG:* Poly: 12 Oligo: 5 Systemic: 1 **Baseline severity:** NR Percentage with uveitis: NR **Inclusion criteria:**	**1) Number of criteria:** At time 0/6 months: SSZ: 7/6 DLG: 4/3 **2) Number of affected joints:** At time 0/6 months: SSZ: 6/5 DLG: 4/3 **3) AM stiffness (minutes)** At time 0/6 months: SSZ: 29/20 DLG: 37/21 **4) Pain score** At time 0/6 months: SSZ: 5/4 DLG: 5/3 **5) Global assessment of current status:** Improved/no effect/worse SSZ: - Physician: 9/9/3 - Patient: 10/7/3 - Parent: 7/11/3 DLG: - Physician: 8/3/7 - Patient: 7/5/3 - Parent: 8/5/5 **5) Laboratory measures of inflammation:**	**General comments:** - Not controlled, not blinded - Poor description of population **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair/poor - Comments: Poor description of patients; unclear if blinded; some outcomes validated, others not; short study duration *Adverse events:* Overall rating: Poor - Comments: Not characterized by patient or treatment received; no n/% given **Applicability:** - Unclear population in terms of age and disease severity - Study outside US - Not blinded

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Primary outcome(s): - Number of JCA criteria - Number of affected joints - Duration of morning stiffness - Pain score - ESR - Functional capacity - Parent/patient and physician global - Improvement (= when 5 of 6 indices reported improved) **Secondary outcome(s):** NR	Pauci or polyarticular JCA **Exclusion criteria:** NR	- ESR at time 0/6 months: SSZ : 52.7/36.3 DLG: 41.2/28.9 **6) Discontinuation of DMARD due to:** NR **7) Mortality:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: SSZ, 4; DLG, 1 **11) Mortality:** 0 **12) Adverse events reported?:** Yes SSZ: 4 (19%) discontinued due to AEs DLG: 1 (5%)	
Ilowite, Porras, Reiff, et al., 2009 **#62**	**Geographical location:** 17 sites in USA, Canada, Australia, New Zealand, and Costa Rica **Study dates:** July 2000 to February 2004 **Funding source:** Amgen, Inc. **Setting:** NR **Study design:** RCT, blinded, placebo-controlled, multicenter, with a 12-week, open-label, run-in period; 16-week, blinded RCT phase; and a 12-month open-label extension period	**Number of patients:** N = 86 in run-in phase, 50 in blinded RCT phase, 30 in extension phase - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 50 - Began treatment: 50 - Completed treatment: 31 - Withdrawals/losses to followup during blinded phase: 19/50 (38%; Anakinra N = 6 [4 for disease flare], placebo N = 13 [10 for disease flare]) Note: Reasons for withdrawal from blinded phase NR **Age:**	**1) Active joint count:** NR **2) Quality of life/functional status:** CHAQ change at week 28: Anakinra: -0.25 Placebo: 0.13 P value NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR change at week 28: Anakinra: -2.21	**General comments:** - Primary outcome changed from efficacy to safety because of low enrollment - Baseline CHAQ and ESR values NR **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Not powered for efficacy; insufficient reporting of randomization and concealment; no validated AE measure; conflict of interest with funding source, run-in phase *Adverse events:*

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	Patients who experienced disease flare during the blinded phase were given the option to switch arms (and remain blinded) **Intervention(s):** - DMARD name: Anakinra - Dose: 1.0 mg/kg/day (max dose 100 mg/day) by daily injection - Titration: NA - N: 86 in run-in phase, 25 in RCT phase (plus 25 who received placebo), and 29 who completed open-label extension phase **Comparator(s):** Placebo (N = 25) **Were additional arthritis medications allowed?:** Yes: NR whether these were added per protocol or at the discretion of study investigators **Study duration:** 12-week run-in phase 16-week blinded phase 12-month extension phase **Primary outcome(s):** Safety, as defined by the incident of treatment-emergent AEs and lab values Assessments done at baseline, week 2, week 4, and every 4 weeks thereafter in blinded phase, then every 3 months in	- Mean (SD): 12 (SD NR) - Range: 3 to 17 **Sex:** - Female: 63 (73%) - Male: 23 (27%) **Race/ethnicity:** White: 46 (53%) Black: 5 (6%) Hispanic: 29 (34%) American Indian/Alaskan native: 3 (3%) Asian: 1 (1%) Other: 2 (2%) **JIA diagnosis:** JRA Anakinra Placebo Onset: N (%) N (%) - Polyarticular 14 (56) 19 (76) - Systemic 9 (36) 2 (8) - Pauciarticular 2 (8) 4 (16) **Baseline severity:** NR **Percentage with uveitis:** NR **Inclusion criteria:** - Presenting with polyarticular-course JRA, independent of onset - Required to have ≥ 5 swollen joints due to active arthritis (not bony overgrowth) and 3 joints with limitation of motion at screening and day 1 visit	Placebo: 13.73 P value NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** By week 28: Anakinra Placebo N (%) N (%) - Polyarticular 2 (14) 8 (42) - Systemic 2 (22) 1 (50) - Pauciarticular 0 1 (25) P = 0.11 "Time to disease flare was greater in patients receiving anakinra, nearly reaching statistical significance (p = 0.057)." **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 27/86 patients (31%) in open-label run-in phase withdrew because of nonresponse - Intolerance/AEs: 4/86 patients (5%) in open-label run -n phase withdrew because of AEs Reasons for withdrawal from blinded phase NR **11) Mortality:** None	- Overall rating: Fair - Comments: Insufficient reporting of randomization and concealment; no validated AE measure; conflict of interest with funding source **Applicability:** Outcomes measured; differential dropout rates (12% vs. 26%)

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	extension phase up to 12 months **Secondary outcome(s):** Response, defined as ≥ 30% improvement in any 3 of 6 JRA core set criteria variables, including: - Physician global assessment of disease activity; - Patient/parent assessment of disease activity; - CHAQ; - Number of joints with active arthritis; - Number of joints with limited range of motion; - ESR. Also assessed: - Proportion of patients with disease flares in the blinded phase; - Time to disease flare; - Changes in the JRA core components at week 28; - Pharmacokinetics.	- Age between 2 and 17 years - Minimum weight of 10 kg - On a stable dose of MTX for 6 weeks before study entry and not receiving biologic therapy within 4 weeks of initiating study drug - Negative pregnancy test of childbearing potential **Exclusion criteria:** - Alanine aminotransferase or aspartate aminotransferase > 2.0 times the upper limit of normal - Creatinine > 1.5 times the upper limit of normal - WBC < 2.0 x 10^9/L - Neutrophil count < 1.5x10^9/L - Platelet count < 150x10^9/L - Receiving treatment with a DMARD other than MTX - Receiving intraarticular or systemic corticosteroid injections within 4 weeks before study entry - Clinically significant systemic disease (such as hepatic, renal, neurological, endocrine, cardiac, gastrointestinal [except NSAID-induced GI problems]) - Hematological disease - Presence of symptoms of systemic disease, such as intermittent fever, rash, hepatosplenomegaly, or pericarditis within 24 weeks of the first dose of anakinra	**12) Adverse events reported?:** Yes **13) Other:** Responders: Anakinra (%) Placebo (%) - Polyarticular: 53 NR - Systemic 73 NR - Pauciarticular 67 NR	

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Kvien, Hoyeraal, and Sanstad, 1985 **#1207**	**Geographical location:** Oslo, Norway **Study dates:** 1979 to 1983 **Funding source:** Norsk Hydro Research Foundation for Rheumatology, Norwegian Women Public Health Association, Astra Syntex Research Foundation at Oslo Sanitersforening Rheumatism Hospital and the Norwegian Medicinal Depot **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Hydroxychloroquine (HC)-Ercoquin - Dose: 5 mg/kg daily, rounded upwards to nearest 25 mg and given twice per day - Titration: Given 9 months then withdrawn - N: 25 - DMARD name: Gold sodium thiomalate (GSTM) - Myocrisin - Dose: 0.7 mg/kg by weekly injection - Titration: After total of 14mg/kg (20 weeks), 0.7mg/kg given monthly through week 50 - N: 23 - DMARD name: D-Penicillamine	**Number of patients:** N = 72 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 72 - Began treatment: 72 - Completed treatment: 44 - Withdrawals/losses to followup: 28 **Age:** - Median: 10.8 years - Range: 3.6 to 15.9 years **Sex:** - Female: 47 (65.3%) - Male: 25 (34.7%) **Race/ethnicity:** NR **JIA diagnosis:** JRA (pauciarticular or polyarticular) **Baseline severity:** Active joint count: 7-9 Duration of disease: Median 16 months (range, 3 to 164) Other: Radiographic erosions or severe growth disturbances in ≥ 1 joint, n = 9 **Percentage with uveitis:** "Chronic iridocyclitis," n = 11 **Inclusion criteria:** - Fulfillment of the diagnostic criteria of JRA - Present pauciarticular or polyarticular disease type - Between 2 and 16 yrs old - Active disease with indication	**1) Active joint count:** Baseline (BL) median and median change values at 12, 24, and 50 weeks: 	Drug	BL	12 wk	24 wk	50 wk
HC	9	-1	-2	-4
GSTM	7	-1	-2	-5
PEN	8.5	-2	-2	-2.5 | P = NS **2) Quality of life/functional status:** "Functional capacity" reported as a 1-20 graphic rating scale – see "Global assessment of current status," below **3) Number of joints with limited range of motion:** Baseline (BL) median and median change values at 12, 24, and 50 weeks: | Drug	BL	12 wk	24 wk	50 wk
HC	3	0	0	0
GSTM	3	0	-1	0
PEN	4	0	-1	-2 | P = NS **4) Global assessment of current status:** By physician (1-20 scale, 20 maximum activity): Baseline (BL) median and median change values at 12, 24, and 50 weeks: | Drug	BL	12 wk	24 wk	50 wk
HC	11	-2	-2.5	-8
GSTM	12	-3	-5	-9
PEN	12	-2	-4	-7.5	 P = NS By physician: HVM ≥ 50% improvement by physician's overall assessment at 12, 24, and 50 weeks	**General comments:** None **Quality assessment:** *Primary outcome:* - Overall rating: Poor - Comments: Allocation concealment not specified; important baseline differences; unclear if outcomes assessed blind to intervention; outcomes not well described *Adverse events:* - Overall rating: Poor - Comments: Allocation concealment not specified; important baseline differences; unclear if outcomes assessed blind to intervention; outcomes not well described **Applicability:** Non-USA

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	(Pen)- Distamin - Dose: Rounded to nearest 25 mg and given twice per day - Titration: 2.5mg/kg weeks 1-4; 5 mg/kg weeks 5-8; 7.5 mg/kg weeks 9-12; 10 mg/kg after week 12 to week 50 - N: 24 **Comparator(s):** Three DMARDs compared, no placebo **Were additional arthritis medications allowed?:** Yes: NSAIDs, preferred to be kept constant; acetaminophen as needed **Study duration:** 50 weeks **Primary outcome(s):** Not stated; outcomes measured at 12, 24, and 50 weeks **Secondary outcome(s):** - Joint counts - Articular indices - Physicians' overall assessment - Goniometric measurements - Various functional tests - Ophthalmological examinations - ESR and other laboratory measures	for use of slow-acting antirheumatic drugs (SAARD), that is, progressive disease with reversible disease manifestations without sufficient effect of NSAID **Exclusion criteria:** - Contraindication for use of either hydroxychloroquine, gold sodium thiomalate, or D-penicillamine - Secondary amyloidosis - Present systemic disease type - Use of either systemic corticosteroids, immunoregulatory drugs, or SAARD during the 6 months prior to the study, or local corticosteroid injections or joint surgery during the preceding 2 months	<table><tr><td>Drug</td><td>12 wk</td><td>24 wk</td><td>50 wk</td></tr><tr><td>HC</td><td>4/25</td><td>9/24</td><td>12/17</td></tr><tr><td>GSTM</td><td>6/19</td><td>8/19</td><td>10/15</td></tr><tr><td>PEN</td><td>0/23</td><td>8/19</td><td>8/12</td></tr></table>P = NS By patient/parent: NR **5) Laboratory measures of inflammation:** - ESR: Baseline (BL) median and median change values at 12, 24, and 50 weeks: <table><tr><td>Drug</td><td>BL</td><td>12 wk</td><td>24 wk</td><td>50 wk</td></tr><tr><td>HC</td><td>28</td><td>-4</td><td>-9.5</td><td>-12</td></tr><tr><td>GSTM</td><td>27</td><td>-7</td><td>-10</td><td>-11</td></tr><tr><td>PEN</td><td>20</td><td>-7</td><td>-6</td><td>-8</td></tr></table>P = NS **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** Pain on movement – Baseline (BL) median and median change values at 12, 24, and 50 weeks: <table><tr><td>Drug</td><td>BL</td><td>12 wk</td><td>24 wk</td><td>50 wk</td></tr><tr><td>HC</td><td>6</td><td>-1</td><td>0</td><td>-1</td></tr><tr><td>GSTM</td><td>4.5</td><td>-1</td><td>-1</td><td>-2</td></tr><tr><td>PEN</td><td>7</td><td>-3</td><td>-2</td><td>-2</td></tr></table>P = NS **8) Clinical remission:** NR **9) Flare of disease:** Withdrawals by week 50 due to disease exacerbation HC: 1 GSTM: 0	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			PEN: 2 **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: HC, 6; GSTM, 4; PEN, 4 - Intolerance/AEs: HC, 0; GSTM, 3; PEN, 6 **11) Mortality:** NR **12) Adverse events reported?:** Yes Number of AEs reported (HC / GSTM / PEN): Dermatitis: 1 / 2 / 1 Stomatitis: 0 / 1 / 0 GI upset: 1 / 0 / 4 Taste disturbances: 0 / 0 / 2 Proteinuria: 0 / 2 / 1 Eosinophilia: 0 / 3 / 0 Thrombocytopenia: 0 / 0 / 3 Antibodies to native DNA: 0 / 0 / 1 Other: 0 / 2 / 4 Withdrawals due to AEs: HC: 0 GSTM: 3 PEN: 6	
Kvien, Hoyeraal, and Sandstad, 1986 **#1188**	**Geographical location:** Oslo, Norway **Study dates:** 1979-83 **Funding source:** Norsk Hydro Research Foundation for Rheumatology, Norwegian Women Public Health Association, Astra Syntex Research Foundation at Oslo Sanitetsforening Rheumatism Hospital, Norwegian Medicinal Depot and Norma and Leon	**Number of patients:** N = 32 (AZA N = 17; PL N = 15) - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 32 - Began treatment: 32 - Completed treatment: NR - Withdrawals/losses to followup: 8 – follow-up rates: Week 8: 15/17 AZA; 15/15 PL Week 16: 13/17 AZA; 11/15 PL **Age:** Median (range):	**1) Active joint count:** Baseline (BL) median and median change values at 8 and 16 weeks: | Drug	BL	8 wk	16 wk
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AZA	17	-5	-7
PL	31	1	-1 | P = 0.45 **2) Quality of life/functional status:** Baseline (BL) median and median change values at 8 and 16 weeks:	**General comments:** Reference 15 in the published report has more information on outcomes assessment **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Allocation concealment not stated; small sample with some potentially important baseline differences and significant dropouts

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Hess' Foundation for Support of Rheumatological Research at Olslo Sanitetsforening Rheumatism Hospital **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Azathioprine (AZA) -Imuran - Dose: 2.5 mg/kg rounded to nearest 12.5 mg, given daily - Titration: NA - N: 17 **Comparator(s):** - Matching Placebo (PL) - N: 15 **Were additional arthritis medications allowed?:** Prednisolone, preferably 0.2 mg/kg at trial start; reduced in 5-8 steps until withdrawal by study end; NSAIDS, preferably maintained at stable dose **Study duration:** 16 weeks **Primary outcome(s):** Not specified **Secondary outcome(s):** Multiple disease activity measures	AZA: 10.2 years (2.4-14.8) Placebo: 9.5 years (4.1-15.0) **Sex:** - Female: AZA 12 (70.6%) Placebo 10 (66.7%) - Male: AZA 5 (29.4%) Placebo 5 (33.3%) **Race/ethnicity:** NR **JIA diagnosis:** JRA **Baseline severity:** Active joint count: 17 AZA; 31 PL Duration of disease: 31 months AZA (range 4-139); 21 months PL (range 3-110) Other (specify): Severe radiographic abnormalities: 8 AZA, 7 PL **Percentage with uveitis:** Chronic iridocyclitis: AZA n = 5; PL n = 3 **Inclusion criteria:** - Required therapy with immunomodulatory drugs - Disease was active and progressive (with severe systemic features and/or with severe articular involvement progressing towards irreversible joint abnormalities) - Insufficient response to previous adequate therapy with slow acting antirheumatic drugs	<table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>5</td><td>-2</td><td>-4</td></tr><tr><td>PL</td><td>6</td><td>0</td><td>0</td></tr></table>P < 0.01 **3) Number of joints with limited range of motion:** Baseline (BL) median and median change values at 8 and 16 weeks: <table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>9</td><td>-1</td><td>-1</td></tr><tr><td>PL</td><td>16</td><td>1</td><td>-2</td></tr></table>P = 0.51 **4) Global assessment of current status:** - By physician (1-20 scale, 20 maximum activity): Baseline (BL) median and median change values at 8 and 16 weeks: <table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>13</td><td>-3</td><td>-5</td></tr><tr><td>PL</td><td>16</td><td>1</td><td>-2</td></tr></table>P = 0.12 - By patient ("subjective total assessment, 1-20, 20 maximum activity"): Baseline (BL) median and median changes at 8 and 16 weeks: <table><tr><td>Drug</td><td>BL</td><td>8 wk</td><td>16 wk</td></tr><tr><td>AZA</td><td>5</td><td>-1</td><td>-2</td></tr><tr><td>PL</td><td>6</td><td>1</td><td>0</td></tr></table>P = 0.02 - By patient – HVM "subjective total assessment improved by ≥ 50%: AZA: 6/15 week 8; 8/13 week 16 PL: 1/15 week 8; 1/11 week 16 P = 0.01	*Adverse events:* - Overall rating: Fair - Comments: No details on AE assessments **Applicability:** Not U.S.A.

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		for 6 months for patients with pauci- and polyarticular disease type - Systemic disease patients were included if their responses to previous therapy with corticosteroids were insufficient **Exclusion criteria:** - Previous use of azathioprine or other immunomodulatory drugs - Evidence of concomitant infectious, hematological, or hepatic disease, or other disorders contraindicating use of immunomodulatory drugs - Probably insufficient cooperation and local followup - Joint surgery or corticosteroid injections (both local or systemic) during a period of 2 months before the study - Alterations of the dose of NSAID or corticosteroid during the 7 days before the study - Lack of assent/consent from the patient/parent to take part in the study	**5) Laboratory measures of inflammation:** - ESR: Patients with ≥ 50% improvement AZA: 3/15 week 8; 4/13 week 16 PL: 3/15 week 8; 2/11 week 16 P = 0.36 - ESR: Patients with ≥ 25% improvement AZA: 8/15 week 8; 4/13 week 16 PL: 4/15 week 8; 4/11 week 16 P = 0.41 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** - Pain on movement (1-20, 20 maximum activity): Baseline median and median changes at 8 and 16 weeks: Drug / BL / 8 wk / 16 wk AZA / 3 / -1 / -2 PL / 7 / 0 / -1 P = 0.10 **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy (exacerbation): 1 AZA; 2 PL - Intolerance/AEs: 3 AZA; 0 PL **11) Mortality:** NR **12) Adverse events reported?:** Yes	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Lahdenne, Vahasalo, and Honkanen, 2003 **#530**	**Geographical location:** Finland **Study dates:** NR **Funding source:** NR **Setting:** NR **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Infliximab or etanercept - Dose: Infliximab 3-4 mg/kg IV at weeks 0, 2, 6, and then 4- to 8-week intervals; etancercept (0.4 mg/kg) subcutaneously twice/week - Titration: NR - N: 24 (14 infliximab, 10 etanercept) **Comparator(s):** Open-label comparison to other DMARD **Were additional arthritis medications allowed?:** Yes: One or more of methotrexate, prednisolone, cyclosporine A, sulfasalazine, hydroxylchloroquine, intraarticular corticosteroid injections, NSAIDs NR whether these were added per protocol or at the discretion of study investigators **Study duration:** 12 months	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 24 - Completed treatment: 18 - Withdrawals/losses to followup: Etancerpt (1 noncompliance – switched to infliximab), infliximab (5 noncompliance or adverse events) **Age:** - Mean (SD): 10.2 (NR) - Median: NR - Range: 3.3-16.3 years **Sex:** - Female: NR - Male: NR **Race/ethnicity:** NR **JIA diagnosis:** Polyarticular JIA **Baseline severity:** Active joint count: Etanercept: 10 (5-19) Infliximab: 13 (6-21) Duration of disease: At least 1 year **Percentage with uveitis:** NR **Inclusion criteria:** Refractory to standard treatment for 1 year **Exclusion criteria:** NR	**1) Active joint count:** Etanercept: -9.5 (95% CI -19 to -3) Infliximab: -11.5 (95% CI -17 to -7.5) P = 0.74 **2) Quality of life/functional status:** CHAQ: Etanercept -0.81 (95% CI -1.44 to -0.19) Infliximab: -0.31 (95%CI -0.75 to -0.25) P = 0.12 **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: Etanercept: -29 (95% CI -52 to -14.5) Infliximab: -35 (95% CI -50.5 to -23.5) P = 0.65 - Patient/Parent: Etanercept: -24.5 (95% CI-50.5 to -7.0) Infliximab: -27.5 (95%CI -47.5 to -12) P = 0.81 ACR Paediatric 50: Etancercept: 3 mo (90%), 6 mo (89%), 12 mo (89%) Infliximab: 3 mo(67%) , 6 mo (83%), 12 mo (78%) ACR Paediatric 75: Etancercept: 3 mo (60%), 6 mo (78%), 12 mo (67%) Infliximab: 3 mo(50%) , 6 mo (58%), 12 mo (67%) **5) Laboratory measures of inflammation:** - ESR: Etancercept: -28.5 (95% CI -51.5 to -15) Infliximab: -25 (95%CI: -36 to -15)	**General comments:** - Drug switching makes it hard to interpret the effect of the drugs individually - Not much reported on the subjects **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: No funding source reported, assessment not masked *Adverse events:* - Overall rating: Fair - Comments: No validated AE measure, no funding source reported **Applicability:** Outcomes measured prospectively

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			P = 0.37 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: 0 - Inefficacy: NR - Intolerance/AEs: 3 in the infliximab group – infusion reaction with chest pain, dyspnea and urticaria which could not be controlled by slowing infusion or premedication 1 in infiximab group – possible macrophage activation syndrome 1 in infliximab group – alopecia 3 in the infliximab group switched to etanercept, which was tolerated **11) Mortality:** None **12) Adverse events reported?:** Yes	
Lovell, Giannini, Reiff, et al., 2000 **#721** **AND** **Lovell, Giannini, Reiff, et**	**Geographical location:** Multiple sites in US and Canada **Study dates:** NR **Funding source:** Supported by Immunex Corporation, Seattle, which provided the study drug and grants to investigational sites; by the Children's Hospital Foundation of Cincinnati; and by grants from the National	**Number of patients:** N = 69 - Screened for inclusion: NR - Eligible for inclusion: NR - Enrolled in lead-in phase: 69 - Completed lead-in phase: 64 - Enrolled in RCT phase: 51 - Began treatment: 51 - Completed treatment: 40 - Withdrawals/losses to followup: Lead-in phase: 5/69 (1 AE, 2 withdrew consent, 2 lack of response)	**1) Active joint count:** Placebo N = 26 / Etanercept N = 25 Baseline: 27.0 / 32.0 3 mo: 37.5 / 13.0 7 mo: 13.0 / 7.0 **2) Quality of life/functional status:** CHAQ score:	**General comments:** - Well designed, executed, and reported study - Some potential for conflict of interest **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
al., 2003 **#547**	Institutes of Health (AR42632 and AR44059-P60 MAMDC). **Setting:** NR **Study design:** RCT, multicenter, double-blind, with open-label lead-in and RCT phases (Lovell et al. #721) and ongoing open-label extension phase with 58 patients (Lovell et al. #547) **Intervention(s):** - DMARD name: Etanercept - Dose: 0.4 mg/kg (up to 25 mg) subcutaneously twice weekly, until disease flare occurred or 4 months elapsed - N: 25 **Comparator(s):** Placebo - N: 26 **Were additional arthritis medications allowed?:** Yes: - MTX was discontinued 14 days and other DMARDs 28 days before start of treatment with etanercept - Intraarticular and soft-tissue corticosteroid injections not permitted during or for 1 month prior to the trial - Stable doses of NSAIDs or low doses of corticosteroids permitted, at discretion of clinician - Pain meds allowed except during the 12 hours before joint	RCT phase, etanercept: 6/25 (24%) withdrew because of disease flare RCT phase, placebo: 18/26 (69%) withdrew because of disease flare, and 1 because of parental withdrew consent - Enrolled in open-label extension phase: 58 - Included in analysis of extension phase: 48 - Withdrawals from extension phase: 10 (suboptimal response 7; lost to followup 1; AEs 1; remission 1) **Age:** - Mean (SD): 10.5 (SD NR) - Range: 4-17 years **Sex:** - Female: 43 (62%) - Male: 26 (38) **Race/ethnicity:** White: 52 (75%) Black: 6 (9%) Hispanic: 9 (13%) Other: 2 (3%) **JIA diagnosis:** JRA Lead-in phase, n (%): - Pauciarticular: 7 (10) - Polyarticular: 40 (58) - Systemic: 22 (32) RCT phase, n (%): - Pauciarticular: 3 (6) - Polyarticular: 31 (61)	Placebo N = 26 / Etanercept N = 25 Baseline 1.3 / 1.6 3 mo 0.4 / 0.9 7 mo 1.2 / 0.8 Lead-in phase: 37% median improvement in scores seen for all patients RCT phase: 54% mean improvement in etanercept vs. no change in placebo group (p = 0.01) **3) Number of joints with limited range of motion:** Placebo N = 26 / Etanercept N = 25 Baseline 6.5 / 8.0 3 mo 1.0 / 2.0 7 mo 4.5 / 1.0 **4) Global assessment of current status:** Physician's global assessment of disease severity: Placebo N = 26 / Etanercept N = 25 Baseline 6 / 7 3 mo 1 / 2 7 mo 5 / 2	**Applicability:** No significant issues

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	assessment	- Systemic: 14 (56)	Patient's or parent's global assessment of overall well-being:	
	Study duration:	**Baseline severity:**	Placebo Etanercept	
	Lead-in phase: 3 months	Active joint count: 28	N = 26 N = 25	
	RCT phase: 4 months	Duration of disease: 5.9 years	Baseline	
			5 5	
	Primary outcome(s):	**Percentage with uveitis:** NR	3 mo	
	Number of patients with disease flare, defined as worsening of ≥ 30% in 3 of 6 response variables, with improvement of ≥ 30% in no more than 1 variable		1 2	
		Inclusion criteria:	7 mo	
		- 4-17 years of age	5 3	
		- Polyarticular JRA		
		- Had active disease despite treatment with NSAIDs and with	**5) Laboratory measures of inflammation:**	
	Secondary outcome(s):		- ESR:	
	Assessments at screening, baseline, day 15, and at the end of each month, with final safety assessment 30 days after discontinuation of study drug	methotrexate at doses of at least 10 mg per square meter of body-surface area per week	Placebo Etanercept	
			N = 26 N = 25	
		- Had normal or nearly normal platelet, white-cell, and neutrophil counts, hepatic amino-transferase levels, and results of renal-function tests	Baseline	
			27 41	
			3 mo	
			12 15	
			7 mo	
			30 18	
		Exclusion criteria:	- CRP:	
		- Pregnant or lactating females (girls with childbearing potential were required to use contraception throughout the study)	Placebo Etanercept	
			N = 26 N = 25	
			Baseline	
			1.8 3.5	
		- Major concurrent medical conditions	3 mo	
			0.3 0.2	
			7 mo	
			3.5 0.4	
			"In the double-blind study as compared with the end of the open-label study, a significant proportion of patients who received placebo had shifts from normal levels of CRP and ESR to above-normal values ($p \leq 0.03$ for each variable)."	
			6) Radiographic evidence of progression	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			of disease: NR **7) Pain control:** - Visual analog scale (0 = best, 10 = worst): Placebo N = 26: Baseline 3.5; 3 mo 0.3; 7 mo 3.5 Etanercept N = 25: Baseline 3.5; 3 mo 1.3; 7 mo 1.5 **8) Clinical remission:** NR **9) Flare of disease:** RCT phase: Placebo: 21 (81%) Etanercept: 7 (28%) P = 0.003 Rates of flare remained consistently and significantly lower in the etanercept group ($p < 0.001$) after adjustment for the effects of baseline characteristics. Median time to flare was > 116 days in the etanercept group, and 28 days in the placebo group ($p < 0.001$). **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 2/69 (3%) in lead-in phase - Intolerance/AEs: 1/69 (2%) in lead-in phase **11) Mortality:** None **12) Adverse events reported?:** Yes	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			13) Other: Definition of improvement: 30% improvement from baseline on ≥ 3 of 6 core variables, with 30% worsening on no more than 1 variable 51/69 (74%) met the definition of improvement at the end of the lead-in phase. 44 (64%) and 25 (36%) met ACR Pedi 50 and ACR Pedi 70 response criteria, respectively At the end of the RCT phase, 18 patients (72%) in the etanercept group and 6 patients (23%) in the placebo group met ACR Pedi 50 criteria for response	
Lovell, Ruperto, Goodman, et al., 2008 **#100**	**Geographical location:** Multiple centers in US, Italy, France, Czech Republic, Belgium, Germany, and the Slovak Republic **Study dates:** Lead-in and RCT phases, Sep 2002 to Jan 2005; ongoing extension phase **Funding source:** Supported by a research grant from Abbott Laboratories **Setting:** NR **Study design:** RCT, double-blind, placebo-controlled, multicenter, medication-withdrawal study, with lead-in, RCT, and extension phases Random allocation, stratified by MTX use (never received MTX	**Number of patients:** N = 171 (85 on MTX, 86 not on MTX) - Screened for inclusion: 196 - Eligible for inclusion: 171 - Open-label lead-in phase: 171 (85 on MTX, 86 not on MTX) - Completed lead-in phase: 160 (83 on MTX, 77 not on MTX) - Began treatment in RCT phase: 133 (75 on MTX, 58 not on MTX) - Completed RCT phase: 128 (71 on MTX, 57 not on MTX) - Entered extension phase: 128 - Withdrawals/losses to followup: Before RCT phase: 38 During RCT phase: 5 **Age:** - Mean (SD): MTX: 11.4 (3.3) No MTX: 11.1 (3.8) - Range: 4-17 years **Sex:**	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR: NR - Other: CPR measured but NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** Defined as > 30% worsening in ≥ 3 of 6	**General comments:** - Very well designed, executed, and reported study - Potential for conflict of interest, given the funding source and the authors' relationships with industry - Allocation concealment not specified **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good **Applicability:** No significant issues

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	vs. discontinued MTX > 2 weeks before) Patients achieving ACR Pedi 30 response at 16 weeks of the lead-in phase entered RCT phase **Intervention(s):** - DMARD name: Adalimumab - Dose: Based on body-surface area during first part of extension phase; in later part, fixed dose given (20 mg for patients weighing < 30 kg, and 40 mg for patients weighing ≥ 30 kg) During lead-in phase: 24 mg/m^2 (up to 40 mg) subcutaneously every other week for 16 weeks - Titration: As above - N: 68 **Comparator(s):** Placebo - N: 65 **Were additional arthritis medications allowed?:** Yes: - Patients taking MTX were at a stable dose of at least 10 mg/m^2/week for 3 months and continued through lead-in and RCT phases - NSAIDs, low-dose corticosteroids, or pain meds given at the discretion of clinician/investigator **Study duration:** 16-week open-label lead-in	- Female: MTX: 68 (80%) No MTX: 67 (78%) - Male: MTX: 17 (20%) No MTX: 19 (22%) **Race/ethnicity:** White: MTX: 81 (95%) No MTX: 76 (88%) Black: MTX: 0 (0%) No MTX: 3 (3%) Other: MTX: 4 (5%) No MTX: 7 (8%) **JIA diagnosis:** JRA, polyarticular **Baseline severity:** Active joint count: - MTX: 15.0 - No MTX: 19.4 Duration of disease, in years: - MTX, placebo: 4.0 - MTX, adalimumab: 4.3 - No MTX, placebo: 2.9 - No MTX, adalimumab: 3.6 **Percentage with uveitis:** NR **Inclusion criteria:** - Age 4-17 years - Polyarticular JRA with active disease - Inadequate response to NSAIDs	core criteria for JRA and improvement of ≥ 30% in no more than 1 criteria No. of disease flares during RCT phase: | Sub-group	Placebo	Adalim	P value
---	---	---	---
MTX	24/37 (65%)	14/38 (37%)	0.02
No MTX	20/28 (71%)	13/30 (43%)	0.03 | **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR During lead-in phase, 1/85 patients (1%) in the MTX stratum and 2/86 (2%) in the no MTX stratum withdrew because of an AE, and 5/85 (6%) in the no MTX stratum withdrew because of lack of efficacy During the RCT phase, 1/133 (1%) withdrew consent, and 4/133 (3%) withdrew for other reasons **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Other:** ACR 30: “The patients improved according to all levels of ACR Pedi response during the open-label lead-in phase.” “More patients treated with adalimumab than patients treated with placebo had ACR Pedi 30, 50, 70, or 90 responses in both the methotrexate stratum and the stratum not receiving MTX.”	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	phase, 32-week RCT withdrawal phase, and ongoing open-label extension phase **Primary outcome(s):** Percentage of patients not receiving MTX who had a disease flare during the RCT phase **Secondary outcome(s):** - ACR Pedi 30, 50, 70, 90, and 100 responses - Safety evaluated on basis of physical exams, lab results, vital signs, and AEs	- Either previously treated with MTX or had AEs or no response to MTX **Exclusion criteria:** - Hematologic, hepatic, or renal abnormalities - Ongoing infection or recent severe infection - Recently vaccinated - Previously treated with IVIG, cytotoxic agents, investigational agents, DMARDs other than MTX, or corticosteroids administered IV, IM, or intraarticular	"During the open-label extension phase, ACR Pedi responses were sustained during 2 years of treatment. After 104 weeks of treatment, 40% of patients had an ACR Pedi 100 response."	
Opper-mann and Mobius, 1994 **#937**	**Geographical location:** Cottbus, Germany **Study dates:** NR **Funding source:** NR **Setting:** NR **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Alphaglobulin (AG) - Dose: 400 mg IG/kg daily x 5 days; repeated 3 days each month for 6-8 months - Titration: None - N: 8 **Comparator(s):** - DMARD name: Methylprednisolone (MP)	**Number of patients:** N = 20 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: NA - Began treatment: 20 - Completed treatment: NR - Withdrawals/losses to followup: NR **Age:** - Range: 2-15 years **Sex:** NR **Race/ethnicity:** NR **JIA diagnosis:** JCA **Baseline severity:** Active joint count: NR Duration of disease: NR **Percentage with uveitis:** NR	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation: (Estimated from graph)** - ESR: MP: Baseline 59, 6 months 21 AG: Baseline 61, 6 months 24 **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Open-label, nonrandomized, analyses not adjusted for baseline differences, patients not adequately described *Adverse events:* - Overall rating: NA - Comments: AEs not reported **Applicability:** Not USA

<table>
<tr><th>Study</th><th>Interventions and study design</th><th>Patient characteristics</th><th>Results</th><th>Comments/ quality/applicability</th></tr>
<tr><td></td><td>- Dose: 30 mg/kg (max 1.0 g/pulse) x 3 days; pulses repeated monthly for 6-8 months
- Titration: None
- N: 12

Were additional arthritis medications allowed?: Yes:
- NSAIDS continued
- Methotrexate 10 mg/m^2/week
- Glucocorticosteroids ≤ 0.2 mg/kg body weight/day – given on alternate days

Study duration: Unclear, likely 6-8 months

Primary outcome(s): NR

Secondary outcome(s):
ESR, CD4, CD8 counts</td><td>Inclusion criteria:
PJCA or SJCA, characterized by high inflammatory activity of the rheumatic process

Exclusion criteria: NR</td><td>9) Flare of disease: NR

10) Discontinuation of DMARD due to:
- Remission of disease: NR
- Inefficacy: NR
- Intolerance/AEs: NR

11) Mortality: NR

12) Adverse events reported?: No</td><td></td></tr>
<tr><td>Prieur, Piussan, Manigne, et al., 1985

#1212</td><td>Geographical location: France

Study dates: NR

Funding source: Supported by Caisse Nationale de l’Assurance Maladie des Travailleurs Salariés

Setting: Outpatient or 3 specialized centers

Study design: RCT, double-blind

Intervention(s):
- DMARD name: D-penicillamine
- Dose: 5 mg/kg/day x 2months
- Titration: Increased to 10 mg/kg/day x 4 months</td><td>Number of patients: N = 74 (DP 38, placebo 36)
- Screened for inclusion: NR
- Eligible for inclusion: 74
- Randomized: 74
- Began treatment: 74
- Completed treatment: 55
- Withdrawals/losses to followup: 12 (4/8)
Analysis complete on 70 (2 misdiagnosed not included)

Age:
- Mean (SD):
DP: 8.2 (3.9)
Placebo: 9.8 (3.9)
- Range: 3-18 years

Sex:</td><td>1) Morning stiffness (minutes, mean [SD]):
<table><tr><td>Drug</td><td>Time 0</td><td>Final</td></tr><tr><td>DPN</td><td>47.5 (36.2)</td><td>26.8 (38.7)</td></tr><tr><td>Placebo</td><td>48.2 (32.5)</td><td>37.2 (43.8)</td></tr></table>
2) Number of painful joints (mean [SD]):
<table><tr><td>Drug</td><td>Time 0</td><td>Final</td></tr><tr><td>DPN</td><td>6.3 (5.5)</td><td>3.3 (3.8)</td></tr><tr><td>Placebo</td><td>7.6 (5.3)</td><td>5.5 (5.5)</td></tr></table>
3) Number of inflamed joints (mean [SD]):
<table><tr><td>Drug</td><td>Time 0</td><td>Final</td></tr><tr><td>DPN</td><td>5.2 (5.2)</td><td>2.5 (3.4)</td></tr><tr><td>Placebo</td><td>2.6 (2.7)</td><td>1.7 (2.1)</td></tr></table></td><td>General comments: None

Quality assessment:
Primary efficacy outcome:
- Overall rating: Fair
- Comments: Outcome measures not validated, patients in placebo group may have had worse disease

Adverse events:
- Overall rating: Good

Applicability: Outdated medication</td></tr>
</table>

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- N: 38 **Comparator(s):** Placebo; N = 36 **Were additional arthritis medications allowed?:** Yes: Pyridoxine hydrochloride 10 mg/kg/day **Study duration:** 6 months **Primary outcome(s):** - Functional Steinbrocker class - Duration morning stiffness (minutes) - Number of painful joints - Number of inflamed joints - Number of stiff joints - Sum of severity of pain - Sum of severity of inflammation - Sum of severity of stiffness - Consumption of steroids and --- - ASA - ESR	- Female: 51 (68.9%) - Male: 23 (31.1%) **Race/ethnicity:** NR **JIA diagnosis:** Polyarticular JCA or pauciarticular JCA (but with polyarticular course) or systemic onset JCA **Baseline severity:** Number of inflamed joints: DPN: 10.5 (± 6.5) Placebo: 13.9(± 19.1) Duration of disease: DPN: 3.1 (± 2.3) Placebo: 4.2 (±3.3) **Percentage with uveitis:** NR **Inclusion criteria:** - Met previously established diagnostic criteria - At least 2 of the following inflammatory criteria: erythrocyte sedimentation rate (ESR) > 25 mm/hour, serum fibrinogen > 400 mg/dL, and elevation (> 2 SD) of IgG, IgA, or IgM **Exclusion criteria:** - Persistence of systemic extraarticular symptoms (mainly spiking fever) during the previous 6 months - Arthritic involvement of < 4 joints - Use of NSAIDs not authorized for pediatric use in France	**4) Number of stiff joints (mean [SD]):** | Drug | Time 0 | Final | | --- | --- | --- | | DPN | 11.7 (9.0) | 8.5 (7.9) | | Placebo | 10.6 (7.5) | 11.1 (9.2) | **5)Severity of pain (mean [SD]):** | Drug | Time 0 | Final | | --- | --- | --- | | DPN | 7.2 (5.8) | 3.6 (4.2) | | Placebo | 8.3 (6.6) | 6.5 (6.3) | **6) Functional class 3-4 (time 0/final):** DPN: 9/4 Placebo: 6/6 **7) Remissions (time final):** DPN: 7 Placebo: 4 **8) ESR (mean [SD]):** | Drug | Time 0 | Final | | --- | --- | --- | | DPN | 49 (32) | 31 (26) | | Placebo | 41 (26) | 33 (23) | **9) Physician/parent/patient assessment** Not completed by all **10) Discontinuation of DMARD due to:** - Remission of disease: 0 - Inefficacy: 1 - Intolerance/AEs: 2 **11) Mortality:** NR **12) Adverse events reported?:** Yes Cytopenia (1)	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		- Systemic corticosteroid therapy > 0.5 mg/kg/day of prednisone or the equivalent -Use of SAARD during the previous 3 months - Any modification of treatment (including physiotherapy) during the past month - Presence of renal, blood, or hepatic disorders during the previous 6 months - History of penicillin allergy	Rash/mouth ulcers (1)	
Riddle, Ryser, Morton ,et al., 2006 **#313**	**Geographical location:** Dallas, Texas **Study dates:** NR **Funding source:** NR **Setting:** Hospital specializing in pediatric rheumatological conditions **Study design:** Nonrandomized comparative study **Intervention(s):** - DMARD name: Methotrexate (MTX) - Dose: NR - Titration: NR - N: 20 **Comparator(s):** - NSAID, dose not specified, n = 22 - Methylprednisolone (MP) IV at time 1 and 4 months later; dose not specified, n = 20	**Number of patients:** N = 57 - Screened for inclusion: NR - Eligible for inclusion: 63 - Randomized: NA - Began treatment: 63 - Completed treatment: 57 - Withdrawals/losses to followup: **Age:** - Mean (SD): 8.1 (4.8) **Sex:** - Female: 44 (77.2%) - Male: 13 (22.8%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Baseline severity:** - Active joint count: Mean of 2.8 to 8.6 across groups - Duration of disease: NR **Percentage with uveitis:** NR **Inclusion criteria:** - Diagnosis of JIA	**1) Active joint count:** Baseline and 4-month mean (SD): NSAID: 2.8 (2.6), 2.0 (2.2) MTX: 8.1 (8.9), 4.1 (5.2) MP: 8.6 (7.3), 1.5 (2.5) F (2, 35) = 5.62, p = 0.008, MP greater percent improvement than other two treatments **2) Quality of life/functional status:** - Generic PedsQL Total Score (Parent report) – Baseline and 4-month mean (SD): NSAID: 76.1 (16.8), 77.5 (17.5) MTX: 69.7 (13.3), 74.7 (15.0) MP: 44.9 (19.4), 72.0 (18.9) Time*Medication F(10, 58) = 2.36, p = 0.02; MP greater percent improvement than other two treatments - Rheumatology PedsQL Total Score (Parent Report) – Baseline and 4-month mean (SD): NSAID: 70.8 (23.5), 75.7 (20.5) MTX: 60.3 (16.9), 71.9 (14.7) MP: 45.9 (19.2), 74.2 (20.1) Time*Medication F(10, 52) = 2.86, p = 0.007; MP greater percent improvement than other two treatments	**General comments:** Patient reports of HRQOL also given **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor - Comments: Confounding by indication; analysis adjusts only for baseline scores and not other potential confounders; outcomes not assessed blind to treatment condition; patients not blind to treatment assignment *Adverse events:* - Overall rating: Fair - Comments: Outcomes not assessed blind to treatment condition; patients not blind to treatment assignment **Applicability:** Poor

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Were additional arthritis medications allowed?: NR **Study duration:** 4 months **Primary outcome(s):** - Pediatric Quality of Life Inventory (PedsQL), version 4.0 -Generic Core Scales - Rheumatology Module, version 3.0 **Secondary outcome(s):** - Adverse effects - Joint counts - ESR - Global assessment	- Beginning new medication treatment – NSAIDs, MTX, or steroids - Age 1-18 years **Exclusion criteria:** - Presence of any other major illness or disability, as determined by the pediatric rheumatologist - Lack of proficiency in the English language prohibiting the administration of study questionnaires	**3) Number of joints with limited range of motion:** Baseline and 4-month mean (SD): NSAID: 3.7 (8.0), 3.1 (7.3) MTX: 7.9 (8.5), 4.3 (6.4) MP: 9.5 (9.3), 3.5 (6.9) **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** ESR – Baseline and 4-month mean (SD): NSAID: 22.6 (22.7), 22.1 (21.3) MTX: 40.2 (30.6), 27.7 (23.4) MP: 77.3 (32.3), 19.3 (18.8) F (2, 35) = 12.3, p = 0.001, MP greater percent improvement than other two treatments **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** Reported only as a subscale of Rheumatology PedsQL **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: NR **11) Mortality:** NR **12) Adverse events reported?:** Yes	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruperto, Lovell, Cuttica, et al., 2007 **#188**	**Geographical location:** 34 sites in North America (9), South America (3), and Europe (22) **Study dates:** Oct 2001 to Apr 2004 **Funding source:** Centocor, Inc. **Setting:** NR **Study design:** RCT, Phase III, international, multicenter, double-blind, placebo-controlled, with double-blind all active treatment extension **Interventions:** DMARD name: Infliximab plus methotrexate Dose: 3 mg/kg Titration: None N: 60 **Comparator:** Placebo + methotrexate for 14 weeks, followed by Inliximab 6 mg/kg plus MTX in weeks 14-52 N: 62 **Were additional arthritis medications allowed:** Yes: Methotrexate 10-15 mg/m^2/week oral or parenteral; other drugs (NSAIDs, opioids, corticosteroids) given at the discretion of the clinician/investigator **Study duration:** 52 weeks	**Number of patients:** N = 122 - Screened for inclusion: NR - Eligible for inclusion: 122 - Randomized: 122 - Began treatment: 122 - Completed treatment: 109 - Withdrawals/losses to followup: 13 (11%) **Age:** Mean (SD): 6 mg/kg: 11.0 (±4.0) 3 mg/kg: 11.3 (±4.0) Range: ≥ 4 to < 18 **Sex:** Female: 6 mg/kg: 49(79.0%) 3 mg/kg: 53(88.3%) Male: 6 mg/kg: 13 (21.0%) 3 mg/kg: 7 (11.7%) **Race/ethnicity:** White: 6mg/kg: 53(88.3%) 3 mg/kg: 50(83.3%) Other: 6 mg/kg: 9 (11.7%) 3 mg/kg: 10 (16.7%) **JIA diagnosis:** JRA Systemic onset: 6 mg/kg: 8 (13.1%) 3 mg/kg: 11 (18.3%) Pauciarticular onset, then polyarticular: 6 mg/kg: 15 (24.6%)	**1) Active joint count:** "At week 14, the number of joints with active arthritis differed significantly between patients in the infliximab 3 mg/kg group and those in the placebo group (p = 0.016), whereas there were no significant differences for the other core set variables." **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** - ESR: NR - Other: NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** 0 active joints at 52 weeks: Infliximab 3mg/kg: 26/59 (44.1%) Placebo then Infliximab 6 mg/kg: 25/58 (43.1%) **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: 9 patients infliximab, 1 placebo + MTX	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Results inconsistently, incompletely, and inadequately reported *Adverse events:* - Overall rating: Fair Comments: Results inconsistently, incompletely, and inadequately reported **Applicability:** Good

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		3 mg/kg: 13 (21.7%)	**11) Mortality:** 2 deaths (1 placebo + MTX, 1 Infliximab)	
	Primary outcome: Proportion meeting ACR Pedi 30 criteria at week 14	Polyarticular: 6 mg/kg: 38 (62.3%) 3 mg/kg: 36 (60%)	**12) Adverse events reported?:** Yes	
	Secondary outcome: - Improvement > 50% and > 70% on Pedi 50 and Pedi 70 - At week 52, number of joints with active disease	**Baseline severity:** Duration of disease (mean years ± SD): 6 mg/kg: 3.6 (± 3.4) 3 mg/kg: 4.2 (±3.6)	**13) Other:** ACR30 (primary study outcome) Week 14: Infliximab 3 mg/kg: 37/58 (63.8%) Placebo + MTX: 29/59 (49.2%) Week 52 (all patients): Pedi 50: 78/112 (69.9%) Pedi 70: 58/112 (51.8%) No significant differences between study groups	
		Active joint count (mean ± SD): 6 mg/kg: 18.5 (± 11.5) 3 mg/kg: 19.5 (± 12.3)		
		Rheumatoid factor + (n [%]): 6 mg/kg: 14 (23.7%) 3 mg/kg: 13 (21.7%)	"By the end of the study, following crossover of placebo-treated patients to infliximab 6 mg/kg, improvement in the JRA core set components was comparable between the treatment groups."	
		Percentage with uveitis: 0%		
		Inclusion criteria: - Age ≥ 4 years and < 18 years - JRA - Suboptimal response to MTX after ≥ 3 months - ≥ 5 active joints - No active systemic symptoms		
		Exclusion criteria: - Active uveitis - Serious infection, including tuberculosis - Malignancy - Prior treatment with TNF inhibitor		

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Ruperto, Lovell, Quartier, et al., 2008 **#102**	**Geographical location:** Europe, Latin America, USA **Study dates:** Feb 2004-June 2006 **Funding source:** Bristol-Myers Squibb **Setting:** Pediatric rheumatology centers **Study design:** Open-label run-in followed by RCT **Intervention(s):** Open label: Abatacept 10mg/kg (max 1000 mg) on days 1, 15, 29, 57, and 85 of the 4-month open-label period Subjects who met ACR-Ped 30 were randomized to abatacept or placebo Abatacept 10mg/kg in 28-day intervals for 6 months or until a flare **Comparator(s):** Placebo (for RCT) **Were additional arthritis medications allowed?:** Methotrexate (if stable on it), folinic or folic acid, stable oral corticosteroids (10 mg/day or 0.2 mg/kg/day, whichever less), NSAIDs or analgesics for pain control	**Number of patients:** - Screened for inclusion: 214 - Eligible for inclusion: 190, of whom 170 enrolled in open-label trial - Randomized: 123 (based on response in open-label trial) - Began treatment: 122 - Completed treatment: 42 discontinued because treatment not effective - Withdrawals/losses to followup: 1 withdrew consent; 80 completed all visits in the 6-month double-blind period **Age:** Mean (SD) for the double-blind period: Abatacept (n = 60): 12.6(3) Placebo (n = 62): 12.0 (3) Overall age range: 6-17 years **Sex:** For the double-blind period Abatacept: - Female: 72% - Male: 28% Placebo: - Female: 73% - Male: 27% **Race/ethnicity:** For the double-blind period Abatacept: - White: 77% - Black: 8% - Other: 15% Placebo: - White: 79%	**1) Active joint count:** At the end of the RCT (mean [SD]): Abatacept: 4.4 (7.0) Placebo: 6.0 (5.8) P = 0.02 **2) Quality of life/functional status:** CHAQ (mean [SD]): Abatacept: 0.8 (0.9) Placebo: 0.7 (0.6) P = 0.04 **3) Number of joints with limited range of motion (mean [SD]):** Abatacept: 8.8 (12.8) Placebo: 8.6 (12.0) P = 0.01 **4) Global assessment of current status:** By physician (mean [SD]): Abatacept: 14.7 (18.9) Placebo: 12.5 (12.5) P < 0.01 By patient/parent (mean [SD]): Abatacept: 17.9 (22.2) Placebo: 23.9 (21.6) P = 0.70 **5) Laboratory measures of inflammation:** ESR (mean [SD]): Abatacept: 25.1 (26.4) Placebo: 30.7 (30.1) P = 0.96 C-reactive protein (mean [SD]): Abatacept: 0.16 (0.25) Placebo: 0.29 (0.54) P = 0.03	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Potential funding conflict *Adverse events:* - Overall rating: Good - Comments: Potential funding conflict **Applicability:** Good

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Study duration: 4 months (open-label), then 6 months (RCT); study also reports a 5-year open-label followup after the RCT component **Primary outcome(s):** Time to flare (30% or more in at least 3 of 6 core variables, with at least 30% improvement in no more than 1 variable) **Secondary outcome(s):** ACR Pediatric 30, 50, 70, and 90	- Black: 7% - Other: 15% **JIA diagnosis:** JIA **Baseline severity:** For the double-blind period (mean [SD]): Active joint count: Abatacept: 18.2 (11.5) Placebo: 14.7 (12.8) Duration of disease: Abatacept: 3.8 (3.7) years Placebo: 3.9 (3.5) years CHAQ disability index: Abatacept: 1.3 (0.7) Placebo: 1.2 (0.8) Parent global assessment: Abatacept: 41.8 (22.5) Placebo: 39.9 (24.7) ESR: Abatacept: 31.4 (27.7) Placebo: 30.8 (26.9) **Percentage with uveitis:** None **Inclusion criteria:** - 6-17 years - JIA - At least 5 active joints - Active disease (at least 2 active joints and 2 joints with limited ROM) - Inadequate response to or intolerance to at least one DMARD (including etanercept, infliximbab, adalimumab)	**6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** Inactive disease in 30% of abatacept vs. 11% controls (p = 0.02) **9) Flare of disease:** By ACR Pediatric 30 criteria, after 6 months of RCT or time of flare for those who did not complete, 82% in the abatacept improved compared with 69% in the placebo (p = 0.17) By ACR Ped 50, 77% in abatacept improved, compared with 52% in controls (p < 0.01) By ACR Ped 70, 53% in abatacept improved, compared with 31% placebo (p = 0.02) By ACR Ped 90, 40% in abatacept improved, compared with 16% in placebo (p < 0.01) **10) Discontinuation of DMARD due to:** - Remission of disease: None during RCT - Inefficacy: 10 - Intolerance/AEs: None during RCT **11) Mortality:** None **12) Adverse events reported?:** Yes During the run-in: 25 headache (13%), 19 nausea (10%), 17 cough (9%), 17 diarrhea (9%), 14 upper respiratory tract infection	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		Exclusion criteria: - Active uveitis - Major concurrent medical conditions - Pregnant or lactating - No live vaccine within 3 months of the first dose of study medication - Intraarticular injections 4 weeks before enrollment or throughout the trial	(7%), 12 fever (6%), 8 infusional AEs During the RCT: No serious AEs for those with abatacept	
Silverman, Cawkwell, Lovell, et al., 1994 **#914**	**Geographical location:** US **Study dates:** NR **Funding source:** Baxter HealthCare, American Red Cross, Children's Hospital Research Foundation of Cincinnati, The Arthritis Foundation **Setting:** 9 sites in the US **Study design:** RCT **Intervention(s):** - DMARD name: IVIG - Dose: 1.5 g/kg, max 75 g every 2 weeks for the first 2 months then monthly for an additional 4 months - Titration: NR - N: 14 **Comparator(s):** Placebo N: 17	**Number of patients:** - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 31 - Began treatment: NR - Completed treatment: 15 - Withdrawals/losses to followup: 1 dropout in placebo group, 1 placebo who did not meet eligibility criteria, 6 in each group because treatment insufficient, 1 in placebo for logistical reasons, 1 due to AE (noninfectious hepatitis) **Age:** IVIG - Mean (SD): 8.85 (1.3) - Median: 8.32 Placebo - Mean (SD): 9.07 (1.2) - Median: 8.53 **Sex:** IVIG - Female: 5 - Male: 9	**1a) Active joint count (mean change [SE], median):** IVIG: 3 (5), -2 Placebo: 1.5 (3.6), -1 **1b) Overall severity (mean change [SE], median):** IVIG: 21.4 (26.5), -5.5 Placebo: 5.1 (18.9), -18 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** By physician: 50% of the IVIG and 27% of the placebo improved ($p > 0.3$) By patient/parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR	**General comments:** - Small sample size led to heterogeneity - High dropout rate (50%) **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Poor. - Comments: Method not described or validated; small sample size *Adverse events:* - Overall rating: Poor - Comments: Rating was used to assign likelihood that the AE was related to IVIG; no AE data reported for the placebo group **Applicability:** Poor (small sample size)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Were additional arthritis medications allowed?: Yes: - No more than 2 NSAIDs and up to 2 SAARDs – NR whether these were given per protocol or at the discretion of the clinician/ investigator; - Corticosteroids: 2 arms, either no steroids or steroid tapering, given per protocol **Study duration:** 6 months **Primary outcome(s):** Physician's global assessment **Secondary outcome(s):** - Joint count - Hemoglobin - Albumin - Platelet count - ESR	Placebo - Female: 7 - Male: 10 **Race/ethnicity:** NR **JIA diagnosis:** Systemic JRA **Baseline severity:** Active joint count: IVIG: 11.8 (3.2) Placebo: 16.8 (3.5) Duration of disease: IVIG: 1.55 (0.8) years Placebo: 1.89 (0.5) years Sum of severity scores for swelling, pain on motion, tenderness, and limitation of motion: IVIG: 48.1 (11.1) Placebo: 78.5 (17.4) **Percentage with uveitis:** NR **Inclusion criteria:** - Active, refractory systemic JRA, - At least 1 day of fever of 38.5 or greater within 30 days before enrollment - At least 1 of the following: Hb < 10.5 g/dL, albumin < 35 mg/dL, ESR > 20 mm/h, platelet count > 450,000 - Active articular disease **Exclusion criteria:** Intraarticular steroids	**8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: None - Inefficacy: 6 in each group - Intolerance/AEs: 1 (IVIG) **11) Mortality:** None **12) Adverse events reported?:** Yes 4 patients in IVIG group had 10 AEs, of which 6 were considered probably or possibly treatment-related. 9/10 were chills, fever, emesis, or headache; 1 was hepatitis. Most AEs were infusion-related.	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
Silverman, Mouy, Spiegel, et al., 2005 **#383**	**Geographical location:** Multinational **Study dates:** NR **Funding source:** Sanofi-Aventis **Setting:** NR **Study design:** RCT **Intervention(s):** - DMARD name: Oral leflunomide - Dose: if < 20 kg, 100 mg loading x 1 day and then 10 mg every other day; if 20-40 kg, 100 mg loading x 2 days, then 10 mg daily; if > 40 kg, loading 100 mg x 3 days, then 20 mg daily **Comparator(s):** Oral methotrexate 0.5 mg/kg/week (max 25 mg), and placebo **Were additional arthritis medications allowed?:** Yes: Folic acid or folinic acid (everyone), NSAIDs, prednisone (in unchanged), up to 2 doses of intraarticular corticosteroid – all given at the discretion of the clinician/investigator **Study duration:** 16 weeks with an optional 32-week extension **Primary outcome(s):**	**Number of patients:** - Screened for inclusion: 103 - Eligible for inclusion: 94 - Randomized: 94 - Began treatment: 47 in each group - Completed treatment: 86 completed 16-week study and 54 completed 48-week extension - Withdrawals/losses to followup: For the 16-week study, 3 in the methotrexate group withdrew (1 AE, 1 lack of efficacy, 1 lost), 5 in the leflunomide group withdrew (3 AEs, 1 lack of efficacy, 1 declined to take drug). For the extension, in the methotrexate group, 7 did not enroll (3 at nonparticipating site, 2 for lack of efficacy, 2 declined consent). In the leflunomide group, 9 did not enroll (4 at nonparticpating site, 4 lack of efficacy, 1 declined consent). **Age:** Leflunomide: - Mean (SD): 10.1 (4.0) - Median: 11 - Range: 3-17 Methotrexate: - Mean (SD): 10.2 (3.8) - Median: 11 - Range: 3-17 **Sex:** Leflunomide: - Female: 75% - Male: 26%	**1) Active joint count:** At 16 weeks: -8.1 in leflunomide group versus -8.9 in methotrexate group (NS) **2) Quality of life/functional status:** At 16 weeks: ACR Pedi 30 responses were 68% in leflunomide and 89% in methotrexate (p = 0.02) Median time to ACR Pedi 30 response was 52 days in leflunomide and 56 days in methotrexate group ACR Pedi 50 responses were 60% in leflunomide and 77% in methotrexate (p = 0.1) ACR Pedi 70 responses were 43% in leflunomide and 60% in methotrexate (p = 0.14) Mean percent improvement index -44.41 for leflunomide and -52.87 for methotrexate (p = 0.18) CHAQ: -0.44 in leflunomide group and -0.39 in methotrexate group Similar findings described for the extension **3) Number of joints with limited range of motion:** -5.2 in leflunomide group vs. -5.3 in methotrexate group (NS) **4) Global assessment of current status:** Change at 16 weeks: By physician: Leflunomide -31.5, methotrexate -32.1 (overlapping 95% CIs)	**General comments:** Lacks placebo group **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Percent improvement index lacks validation *Adverse events:* - Overall rating: Good **Applicability:** Good

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- ACR Pedi 30 - Percent Improvement Index (mean of the percent changes from baseline in each core set of disease activity measures, with negative values indicating improvement and positive values set to 0 indicating no improvement) **Secondary outcome(s):** - Rates of ACR Pedi 50 and ACR Pedi 70 responses - Time to an ACR Pedi 30 response - Area under the curve analyses - Mean changes in the core set of disease activity measures and - C-reactive protein concentrations	Methotrexate: - Female: 72% - Male: 28% **Race/ethnicity:** Leflunomide: - White: 87% - Black: 2% - Asian: 2% - Other: 9% Methotrexate: - White: 74% - Black: 4% - Asian: 0% - Other: 21% **JIA diagnosis:** JRA **Baseline severity:** Active joint count: - Leflunomide: 14.4 (7.9) - Methotrexate: 14.0 (9.9) Duration of disease: - Leflunomide: 1.69 (3.21) - Methotrexate: 1.37 (1.97) ESR: - Leflunomide: 30.8 (18.2) - Methotrexate: 34.5 (21.7) **Percentage with uveitis:** NR **Inclusion criteria:** - Active polyarticular disease - Not received methotrexate or leflunomide - Sexually active female patients	By patient/parent: Leflunomide -15.9 methotrexate -22.0 **5) Laboratory measures of inflammation:** ESR: Decrease in leflunomide group -6.5; decrease in methotrexate group -7.2 (non-significant) C-reactive protein: decreased -3.9 in leflunomide group vs. -11.4 in methotrexate group (p = 0.04) **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 1 in methotrexate group and 1 in leflunomide group during the first 16 weeks; 2 in the methotrexate group during the extension; 4 in the leflunomide group during the extension - Intolerance/AEs: 1 in the methotrexate group during the first 16 weeks, 3 in the leflunomide group during the first 16 weeks **11) Mortality:** None **12) Adverse events reported?:** Yes In the first 16 weeks leading to withdrawal: 1 methotrexate = LFT abnormalities 1 leflunomide = LFT abnormalities 1 leflunomide = parapsoriasis	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
		negative serum pregnancy studies throughout the study **Exclusion criteria:** - ACR Functional class IV disease - Active systemic symptoms within 4 weeks before entry - Persistent or severe infection within 3 months before entry - Inflammatory disease other then JRA or a history of such a disease	1 leflunomide = Crohn's disease (not thought to be related) Other serious AEs Leflunomide: 1 with suspected salmonellosis None in the methotrexate group	
Smith, Thompson, Whitcup, et al., 2005 **#400**	**Geographical location:** Bethesda, MD **Study dates:** Sep 17,1999-Sep 28, 2001 (enrollment) **Funding source:** Immunex Corp **Setting:** NIH **Study design:** 1year duration – 2 phases: 1st phase: RCT, double-blind 2nd phase: Single arm, open-label Randomized 2:1 etanercept/placebo **Interventions:** DMARD name: Etanercept Dose: 0.4mg/kg twice weekly N: 7 **Comparator:** Placebo N: 5	**Number of patients:** N = 12 - Screened for inclusion: 24 - Eligible for inclusion: 12 - Randomized: 12 (7 to DMARD, 5 to placebo) - Began treatment: 12 - Completed treatment: 12 - Withdrawals/losses to followup: 0 **Age:** Mean (SD): 11 Median: 11 Range: 6-15 years **Sex:** Female: 9 (75%) Male: 3 (25%) **Race/ethnicity:** Hispanic: 4 (33.3%) Black: 1 (8.3%) White: 6 (50%) Pacific Islander: 1 (8.3%) **JIA diagnosis:** JRA	**1) Active joint count:** NR **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** NR **4) Global assessment of current status:** - Physician: NR - Patient/Parent: NR **5) Laboratory measures of inflammation:** NR **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: 1 - Intolerance/AE: 0	**General comments:** - Uveitis patients only - Pilot study **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Small sample size; potential conflict from sponsor *Adverse events:* Fair - Comments: Small sample size; potential conflict from sponsor **Applicability:** All uveitis patients; only ophthalmic outcomes

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Were additional arthritis medications allowed: Yes, if stable MTX and prednisone and at the discretion of the clinician/investigator **Study Duration:** 1 year **Primary outcome:** Ophthalmic outcomes: - Reduction of anterior chamber cells to 0 or trace while using steroids < 3x/day - 50% reduction in number or dose of other anti-inflammatory medication **Secondary outcomes:** - 10-letter change in best corrected visual acuity - 2-step change in anterior chamber cell count, vitreous haze, or anterior chamber cells - Presence of cystoid macular edema	**Baseline severity:** NR **Percentage with uveitis:** 100% **Inclusion criteria:** - 2-18 years of age - ACR criteria for JRA - Active uveitis - No change in arthritis meds for at least 8 weeks prior **Exclusion criteria:** - Media opacities - Periocular injections of steroids within 2 months - DMARD therapy except MTX or prednisone - Spondylarthropathy/enthesitis	**11) Mortality:** None **12) Adverse events reported?:** Yes **13) Ophthalmic outcomes:** Successful outcome: 6 months DMARD: 6/12 12 months DMARD: 4/7 6 months placebo: 2/5 Failures: 6 months DMARD: 1/12 12 months DMARD: 1/7 6 months placebo: 1/5	
Van Rossum, Fiselier, Franssen, et al., 1998 **#798**	**Geographical location:** 7 pediatric rheumatology centers in The Netherlands **Study dates:** Aug 1992 – Dec 1994 **Funding source:** NR **Setting:** Pediatric rheumatology centers **Study design:** RCT **Intervention(s):**	**Number of patients:** N = 69 - Screened for inclusion: NR - Eligible for inclusion: NR - Randomized: 69 - Began treatment: 69 - Completed treatment: 52 - Withdrawals/losses to followup: 17 (1 excluded postrandomization, not eligible) **Age:** - Mean (SD): SSZ: 8.4 (4.4) Placebo 9.7 (3.6)	**1) Active joint count:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments): SSZ: -5.54 (1.16) PL: -0.78 (1.22) P = 0.005 **2) Quality of life/functional status:** NR **3) Number of joints with limited range of motion:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments):	**General comments:** Pain scores not reported, but number of painful joints reported **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good *Adverse events:* - Overall rating: Good **Applicability:** Non-USA

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	- DMARD name: Sulfasalazine (SSZ) - Dose: 50 mg/kg/day in 2 doses; max 2000 mg/day - Titration: ¼ total dose, increased weekly by ¼'s until target dose reached. Dose could be modified to highest dose tolerated, but no less than 50% of initial prescribed dose. - N: 35 **Comparator(s):** Placebo, N = 34 **Were additional arthritis medications allowed?:** Yes - NSAIDS continued in type and dose - Corticosteroids (oral or intraarticular) and other DMARDS not permitted - Other therapy considered necessary for patient's welfare allowed at the discretion of the clinician/investigator **Study duration:** 24 weeks **Primary outcome(s):** Response, defined as ≥ 2 grade improvement in joint swelling severity score or score of 0 in ≥ 50% of joints involved at baseline and, if applicable, development of disease activity in ≤ 10% of the other joints, with the restriction that the number of deteriorated joints had to be ≤ 50% of the number of improved joints	- Range: SSZ: 2.5-17.6 Placebo: 2.5-15.1 **Sex:** - Female: SSZ: 23 (66%) Placebo: 23 (68%) - Male: SSZ: 12 (34%) Placebo: 11 (32%) **Race/ethnicity:** NR **JIA diagnosis:** JCA **Baseline severity:** Active joint count (median [range]): 5 (2-11) SSZ; 7 (3-12) PL **Percentage with uveitis:** NR **Inclusion criteria:** - Met EULAR criteria for oligoarticular- or polyarticular-onset JCA - Age between 2-18 years, with onset of JCA before age 16 - At least 1 joint with active arthritis (defined as the presence of swelling or limitation of motion, with either pain on movement or tenderness) - An insufficient response to NSAID therapy at an optimal dosage for at least 3 months and, if applicable, to intraarticular corticosteroid injections - Intraarticular corticosteroid	SSZ: -2.49 (1.12) PL: -1.97 (0.80) P = 0.64 **4) Global assessment of current status:** Mean (SEM) change (uncertain if this is baseline to 24 weeks or incorporates all assessments): By physician: SSZ: -1.95 (0.18) PL: -0.99 (0.19) P = 0.0002 By patient: SSZ: -0.92 (0.18) PL: -0.24 (0.18) P = 0.008 By parent: SSZ: -0.98 (0.14) PL: -0.44 (0.16) P = 0.010 **5) Laboratory measures of inflammation:** ESR (mm/hour): SSZ: -0.74 (0.07) PL: -0.04 (0.08) P < 0.0001 - Other: CRP given **6) Radiographic evidence of progression of disease:** Mean number of improved joints: SSZ: 0.71 (range, 0-3) PL: 0.53 (range 0-3) P = NS **7) Pain control:** NR	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	Secondary outcome(s): - Overall articular severity score (sum of swelling, tenderness/pain and limitation of movement scores) - Patient's general impression of disease activity (1-5) - Parent's general impression of disease activity (1-5) - Physician's general impression of disease activity (0-5) - ESR, C-reactive protein - Radiological evaluation	injections were not permitted 8 weeks prior to the start of the study - There was a 4-week washout period for DMARDs **Exclusion criteria:** - Previous treatment with SSZ - Known hypersensitivity to sulfa preparations or salicylates - Known glucose-6-phosphate dehydrogenase deficiency or porphyria - Leukopenia < 3.0a10^9/L or granulopenia < 1.0x10^9/L or thrombocytopenia < 100x10^9/L - Liver transaminase levels more than twice the upper limit of normal - Renal impairment, defined as creatinine clearance < 90 mL/minute/1.73m^2 (determined as an elevated serum creatinine level more than 2 SD above the mean value for age) - Unwillingness or inability of parent/children to adhere to the protocol - Females who might become pregnant and if sexually active, not practicing effective birth control	**8) Clinical remission ("response"):** Can be estimated from graph at multiple time points. At 24 weeks: SSZ: 69% (9% SEM) PL: 45% (9% SEM) No significant difference for oligoarticular- and polyarticular-onset patients. Pavia criteria for improvement: SSZ: 44% (9% SEM) PL: 21% (8% SEM) **9) Flare of disease:** NR **10) Discontinuation of DNRMARD due to:** - Remission of disease: NR - Inefficacy: 3 (all PL) - Intolerance/AEs: 10 (all on SSZ) **11) Mortality:** NR **12) Adverse events reported?:** Yes **13) Medication compliance:** > 80% for 83% of subjects	
Woo, South-wood, Prieur, et al., 2000 **#693**	**Geographical location:** UK and France **Study dates:** NR **Funding source:** Supported by Arthritis Research Campaign grant WO-120; MTX and placebo	**Number of patients:** N = 88 - Screened for inclusion: NR - Eligible for inclusion: 88 - Randomized: 88 - Began treatment: 88 - Completed treatment: 79 - Withdrawals/losses to followup: 9 (7 from systemic group, 2 from	**1) Global assessment of current status:** When analyzed separately, no statistically significant differences between MTX and placebo; when combined, statistically significant improvement with MTX *Assessment by physician:* MTX (EOA/systemic):	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Good - Comments: Cross-over with adequate washout; validated outcomes

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	tablets provided by Lederle Laboratories **Setting:** NR **Study design:** RCT, double-blind, cross-over design **Intervention(s):** - DMARD name: Methotrexate - Dose: 15 mg/m^2 PO weekly - Titration: increase to 20 mg/m^2 after 2 months if no improvements in global - N: Goal 44 per group; actual 43 and 45 **Comparator(s):** Placebo **Were additional arthritis medications allowed?:** Yes: Prednisolone, steroid injections, and NSAIDs NR whether these were added per protocol or at the discretion of clinician/investigator **Study duration:** 12 months (4 months treatment, 2 months washout, 4 months treatment, 2 months washout) **Primary outcome(s):** - > 30% improvement in 3 or more core variables and > 30% worsening in no more than 1 Core clinical variables: Physician	EOA = extended oligoarticular arthritis) **Age:** - Mean ± SD (range): EOA: Male: 7.4 ± 3.0 (5.0-11.7) Female: 8.53 ± 3.43 (3.3-15.5) Systemic: Male: 8.5 ± 3.3 (3.7-14.1) Female: 8.0 ± 4.25 (2.5-15.7) **Sex (male):** EOA: 5 (12%) Systemic: 22 (49%) **Race/ethnicity:** NR **JIA diagnosis:** JIA: extended oligoarticular and systemic **Baseline severity:** Active arthritis in past 3 months: EOA: 45 (100%) Systemic: 43 (96%) Duration of disease (months): EOA: 53.8 (4-132) Systemic: 33.7 (4-116) **Percentage with uveitis:** NR **Inclusion criteria:** - Under 16 years of age - Fulfilled the ILAR/WHO criteria for systemic or extended oligoarticular arthritis **Exclusion criteria:** NR	Very active: 28%/28%, -23/-15 Mildly active: 21/28%, +50/+43 Placebo (EOA/systemic) Very active: 24%/33%, -6/-14 Mildly active: 32/23%, +11/+10 P < 0.001 *Assessment by parent:* MTX (EOA/systemic): Very active: 29%/26%, -22/-15 Mildly active: 19/32%, +50/+35 Placebo (EOA/systemic): Very active: 29%/30%, -14/-19 Mildly active: 27/32%, +11/+4 P < 0.001 *Assessment by patient:* MTX (EOA/systemic): Very active: 28%/31%, -18/-24 Mildly active: 13/41%, +39/+28 Placebo (EOA/systemic) Very active: 26%/31%, -13/-17 Mildly active: 29/24%, +11/10 *Systemic core features (outcome = systemic score of 0):* MTX (start/end): 32%/61% Placebo (start/end): 27%/45% **2) Limited joint range:** Treatment effect (mean [SEM]): EOM: 4.47 (3.67) Systemic: 2.57 (6.68) **3) Limited joint score:** Treatment effect (mean [SEM]): EOA: -3.0 (1.8)	*Adverse events:* - Overall rating: Good **Applicability:** - Study outside US- may be more homogeneous population - Long duration of disease at baseline (average 3-4.4 years)

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	global, parent/child global, number of joints with active disease, range of joint motion For systemics, 8 core measures were: Rash; fever; cervical, axillary, ingunial lymphadenopathy; hepatomegaly; splenomegaly; pericarditis **Secondary outcome(s):** - Steroid dose - For systemics, presence of systemic features		Systemic: -3.3 (3.5) **4) Laboratory measures of inflammation:** ESR (baseline mean [SD], treatment effect mean [SEM]): EOA: 49 (28), -16.6 (3.6) Systemic: 57 (31), -12.4 (6.5) C-reactive protein (baseline mean, treatment effect mean [SEM]): EOA: 2.7, -45% (-27%) Systemic: 6.9, -29%(-51%) **5) Steroid dose (mg/day, baseline mean [SD], treatment effect mean [SEM]):** EOM: 1.2 (2.4), -0.012 (0.012) Systemic: 11.6 (6.5), -0.55 (0.92) **6) Overall clinical improvement (MTX/placebo)** EOA: 48/18 Systemic: 25/16 **7) Discontinuation of DMARD due to:** - Inefficacy: 6 systemic, 1 EOA - Intolerance/AEs: 1 systemic, 1 EOA **8) Mortality:** NR **9) Adverse events reported?:** Yes	
Yokota, Imagawa, Mori, et al., 2008 **#138**	**Geographical location:** Japan **Study dates:** NR **Funding source:** Chugai Pharmaceuticals supplied study medication and was responsible for data processing and management, statistical analysis, and reporting of serious adverse	**Number of patients:** N = 56 - Screened for inclusion: NR - Eligible for inclusion: NR - Began lead-in phase: 56 - Completed lead-in phase: 50 - Randomized: 44 - Began RCT phase: 43 (23 placebo; 20 tocilizumab) - Completed RCT: 41 - Began extension phase: 50 (44	**1) Active joint count, median (range):** - Lead-in phase: - Baseline: 4 (0-39) - 6 weeks: 0 (0-34) - Improvement: 73% - RCT, placebo (N = 23): - Baseline: 4 (0-21) - Last observation: 0 (0-34) - RCT, tocilizumab (N = 20): - Baseline: 3.5 (0-18)	**General comments:** None **Quality assessment:** *Primary efficacy outcome:* - Overall rating: Fair - Comments: Potential for significant conflict of interest, given that the data were analyzed by the sponsor of the study, which has a financial interest in tocilizumab;

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	events **Setting:** 8 university hospitals and children's hospitals in Japan **Study design:** RCT, double-blind, multicenter, withdrawal design **Intervention(s):** - DMARD name: Tocilizumab - Dose: 8 mg/kg IV every 2 weeks - Titration: None - N: 20 **Comparator(s):** Placebo - N: 23 **Were additional arthritis medications allowed?:** Some: - Not allowed: Intraarticular corticosteroids, methylprednisolone, immunosuppressive drugs, TNF agents, and other DMARDs - Doses of oral corticosteroids had to be stable for 2 weeks before the trial **Study duration:** Open-label lead-in phase: 6 weeks RCT phase: 12 weeks Open-label extension phase: 48 weeks Patients had to achieve an ACR Pedi 30 response and CRP	randomized, plus 6 not randomized) - Withdrawals: - Lead-in phase: 6/56 (3 antibodies; 2 AEs; 1 lack of efficacy) - RCT placebo: 19 (1 AE; 18 early escape) - RCT tocilizumab: 4 (1 AE; 3 early escape) - Extension phase: 2 withdrawn because of AE - Loss to followup: 0 **Age:** - Mean (SD): 8.3 (4.4) - Range: 2-19 years **Sex:** - Female: 35 (62.5%) - Male: 21 (37.5%) **Race/ethnicity:** NR **JIA diagnosis:** JIA **Baseline severity:** Active joint count (median [range]): Start of lead-in phase: 4 (0-39) Start of RCT phase, placebo: 4 (0-21) Start of RCT phase, tocilizumab: 3.5 (0-18) Duration of disease, years (SD): Placebo: 4.7 (4.0) Tocilizumab: 4.6 (3.5) Past treatments (number [SD]):	- Last observation: 0 (0-4) - Extension phase: - 48 weeks: 0 (0-4) - Improvement: 88% **2) Quality of life/functional status:** CHAQ score, median (range): - Lead-in phase: - Baseline: 0.88 (0-3) - 6 weeks: 0.38 (0-3) - Improvement: 43% - RCT, placebo (N = 23): - Baseline: 0.63 (0-3) - Last observation: 0.38 (0-3) - RCT, tocilizumab (N = 20): - Baseline: 0.88 (0-2.38) - Last observation: 0.38 (0-1.63) - Extension phase: - 48 weeks: 0.13 (0-2.13) - Improvement: 67% **3) Number of joints with limited range of motion, median (range):** - Lead-in phase: - Baseline: 0.5 (0-47) - 6 weeks: 0 (0-45) - Improvement: 54% - RCT, placebo (N = 23): - Baseline: 0 (0-37) - Last observation: 0 (0-42) - RCT, tocilizumab (N = 20): - Baseline: 0.5 (0-47) - Last observation: 0 (0-46) - Extension phase: - 48 weeks: 0 (0-62) - Improvement: 72% **4) Global assessment of current status:** - Physician, visual analog scale, 0 mm (best) to 100 mm (worst), median (range):	screening and randomization procedures not described *Adverse events:* - Overall rating: Fair - Comments: Same issues as above **Applicability:** No significant issues

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
	concentrations < 5 mg/L at end of lead-in phase to be eligible for RCT phase **Primary outcome(s):** Proportion of patients who maintained an ACR Pedi 30 response and CRP concentrations < 15 mg/L **Secondary outcome(s):** - ACR Pedi responses, systemic feature score, and CRP assessed every 2 weeks - Active disease defined by an increase in CRP and an inadequate response to corticosteroids for longer than 3 months - Safety monitored by physical exam daily during hospital stay	Placebo: 2.0 (1.0) Tocilizumab: 2.1 (1.0) **Percentage with uveitis:** NR **Inclusion criteria:** - 2-19 years of age - Onset of disease before 16th birthday - Met the ILAR classification criteria for systemic-onset JIA **Exclusion criteria:** - Important concurrent medical or surgical disorders - Leucopenia (< $3.5x10^9$/L) or thrombocytopenia (< $100x10^9$/L) - Cardiac disease (assessed by a pediatric cardiologist before enrollment) - Developed macrophage-activation syndrome during the prestudy hospital admission	- Lead-in phase: - Baseline: 52 (18-100) - 6 weeks: 8.5 (0-97) - Improvement: 75% - RCT, placebo (N = 23): - Baseline: 51 (18-95) - Last observation: 14 (0-84) - RCT, tocilizumab (N = 20): - Baseline: 51.0 (21-96) - Last observation: 5.5 (0-47) - Extension phase: - 48 weeks: 3.5 (0-22) - Improvement: 89% - Patient or parent's, visual analog scale, 0 mm (best) to 100 mm (worst), median (range): - Lead-in phase: - Baseline: 53 (0-90) - 6 weeks: 13.5 (0-69) - Improvement: 63% - RCT, placebo (N = 23): - Baseline: 55 (18-85) - Last observation: 39 (2-94) - RCT, tocilizumab (N = 20): - Baseline: 51.5 (0-76) - Last observation: 4.5 (0-34) - Extension phase: - 48 weeks: 8.5 (0-70) - Improvement: 75% **5) Laboratory measures of inflammation:** - ESR, mm/h (range): - Lead-in phase: - Baseline: 44.5 (8-125) - 6 weeks: 4.0 (0-64) - Improvement: 82% - RCT, placebo (N = 23): - Baseline: 35 (8-68) - Last observation: 11 (1-41)	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			- RCT, tocilizumab (N = 20): - Baseline: 39.5 (8-103) - Last observation: 4.0 (0-7) - Extension phase: - 48 weeks: 3.0 (0-12) - Improvement: 91% - CRP, mg/L (range): - Lead-in phase: - Baseline: 43.5 (16-190) - 6 weeks: 0.5 (0-99) - Improvement: 90% - RCT, placebo (N = 23): - Baseline: 38 (17-131) - Last observation: 15 (0-101) - RCT, tocilizumab (N = 20): - Baseline: 35 (16-190) - Last observation: 0.1 (0-22) - Extension phase: - 48 weeks: 0.1 (0-2) - Improvement: 99% **6) Radiographic evidence of progression of disease:** NR **7) Pain control:** NR **8) Clinical remission:** NR **9) Flare of disease:** NR **10) Discontinuation of DMARD due to:** - Remission of disease: NR - Inefficacy: NR - Intolerance/AEs: Lead-in phase: 2/56 (4%); RCT placebo: 1/23 (5%); RCT tocilizumab: 1/20 (5%) Early escape (switched to another medication due to poor response):	

Study	Interventions and study design	Patient characteristics	Results	Comments/ quality/applicability
			- Placebo: 18/23 (78%) - Tocilizumab: 3/20 (15%) "Median time to early escape was 4.9 weeks in the placebo group, but longer than 12 weeks in the tocilizumab group" (significance test NR) **11) Mortality:** None **12) Adverse events reported?:** Yes **13) Other:** ACR Pedi Responses: - Lead-in phase, N (%): - ACR Pedi 30: 51 (91%) - ACR Pedi 50: 38 (86%) - ACR Pedi 70: 38 (68%) - Both ACR Pedi 30 response and CRP < 5 mg/L: 44 (79%)	