Paediatric and Adolescent Rheumatology

An Update

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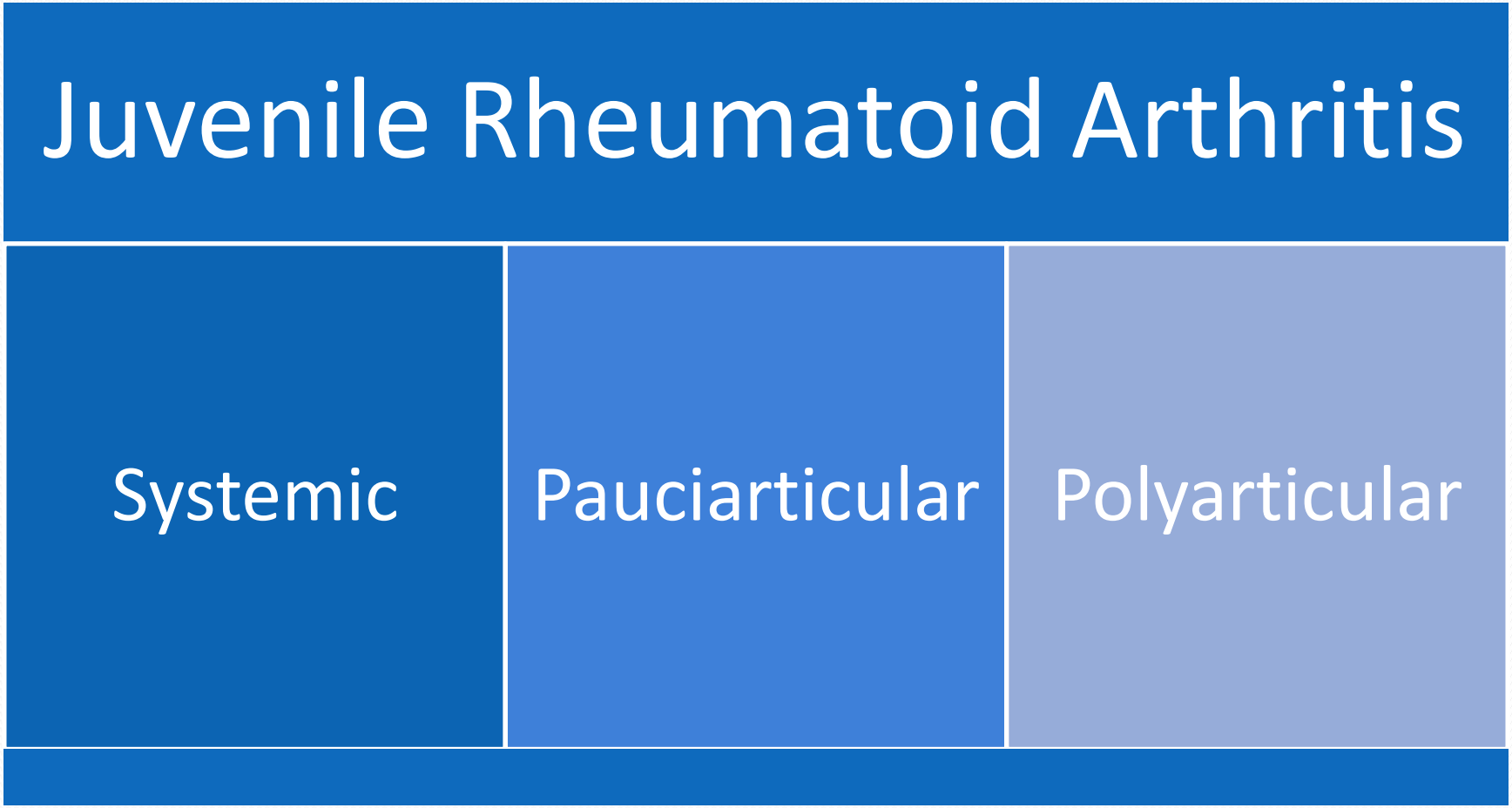
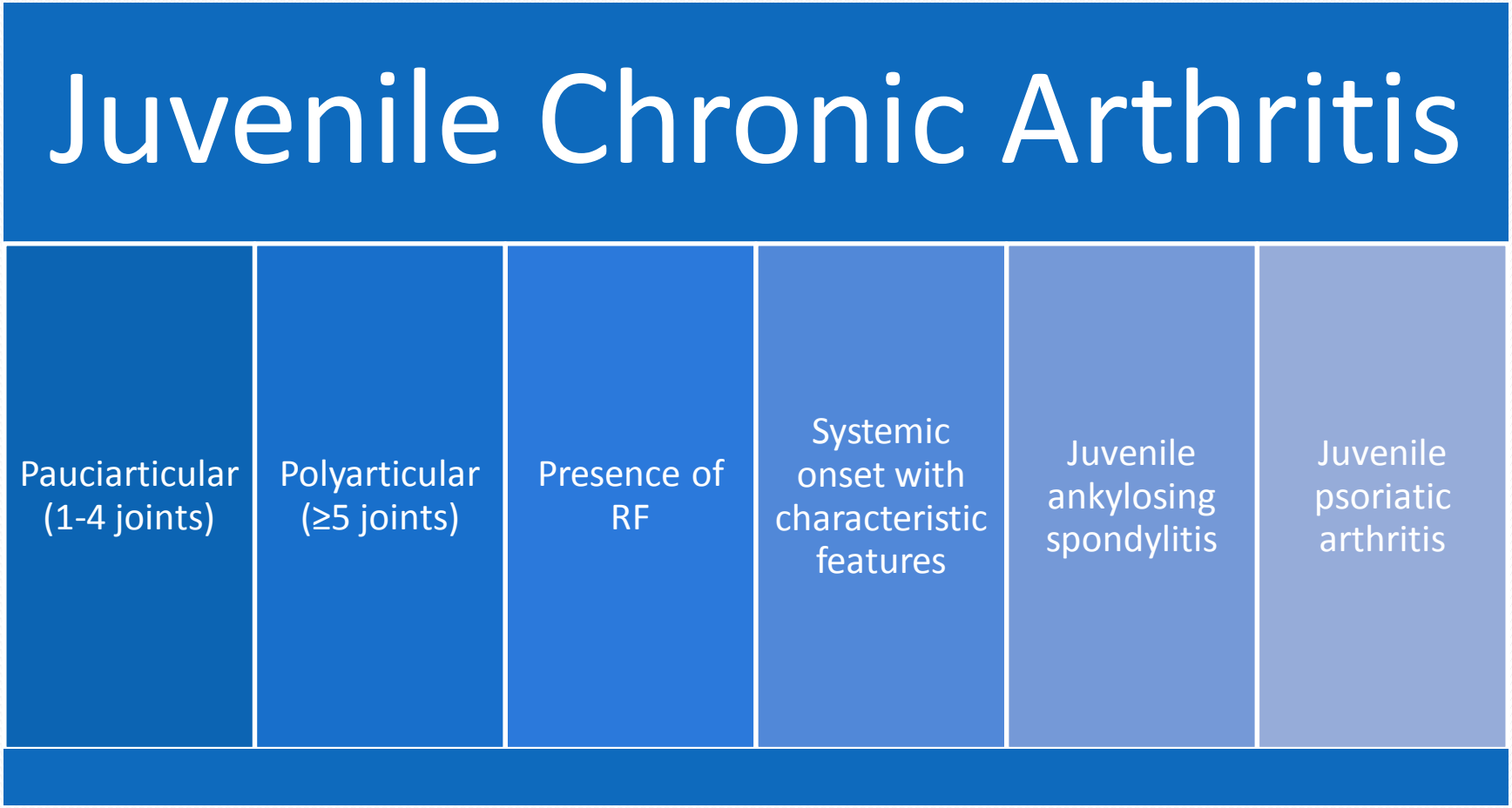
June 2012

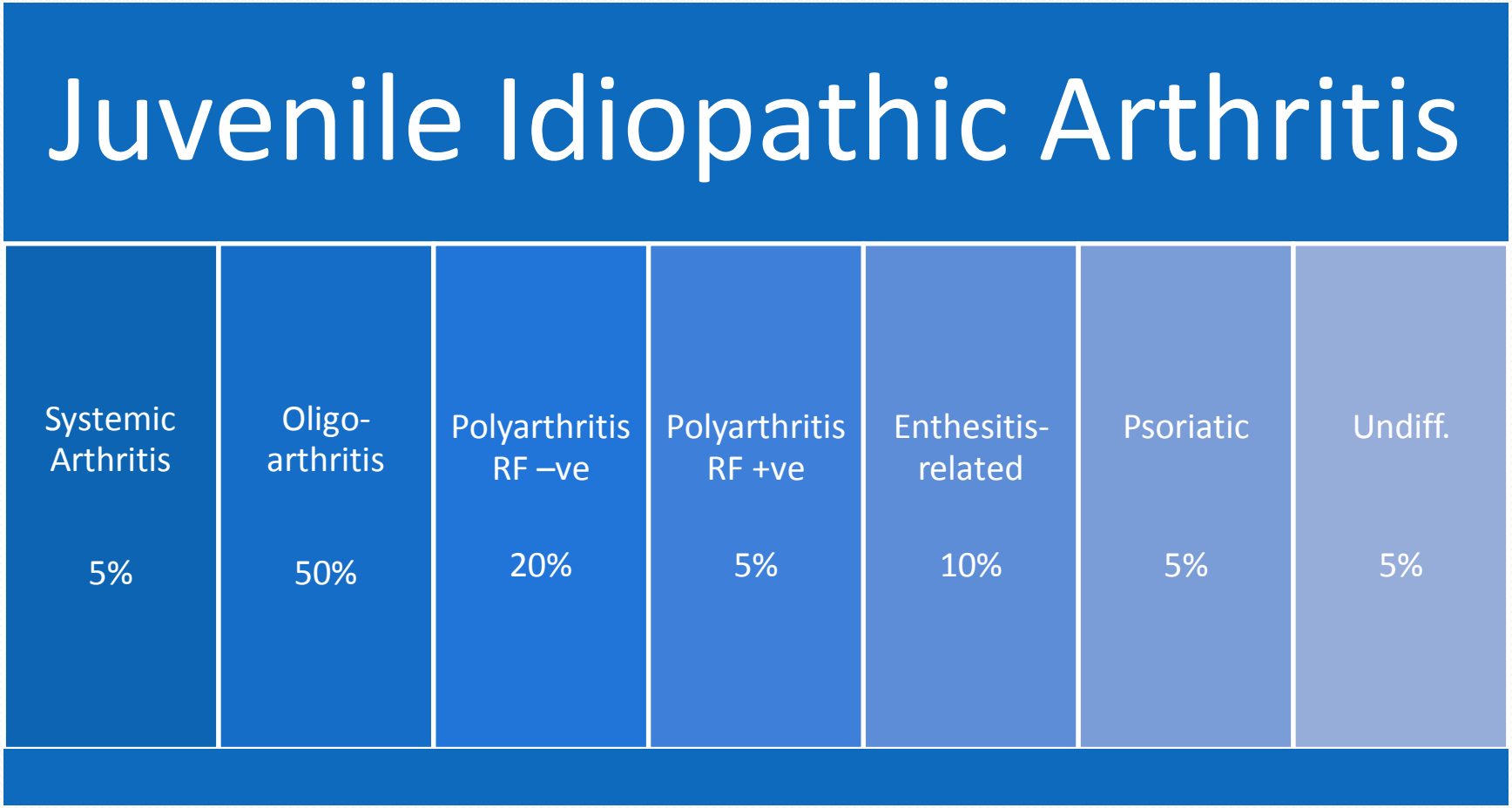
ACR Classification (1977)



EULAR Classification (1977)



ILAR Classification (1997)



Juvenile Idiopathic Arthritis

- Arthritis of unknown etiology that begins before the 16th birthday and persists for at least 6 weeks

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

JIA in the UK

- Incidence 1:10,000
- Prevalence 1:1000

Complication #1

- Uveitis
  - 8-30% in JIA overall
  - Up to 50% in oligoarticular
  - Often clinically silent
  - Most common complications:
    - Cataracts (20%), synechiae (20%), glaucoma (15%), band keratopathy (14%) and macular edema (5%).
  - Predictors
    - ANA positive, age <6 at diagnosis, severity of disease, male gender

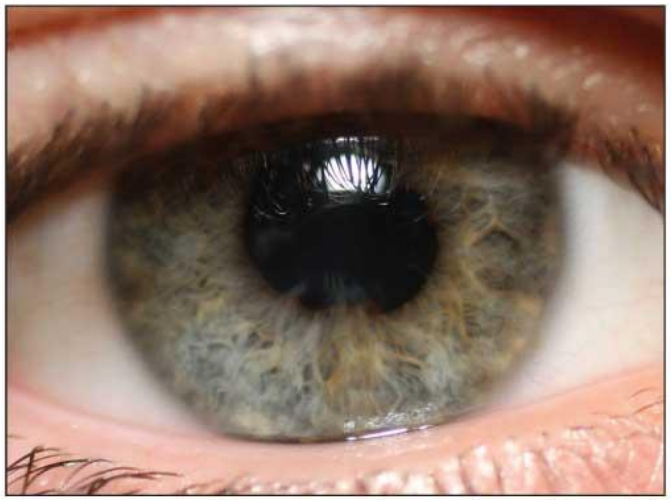


Figure 1 – *Synechiae are seen in a patient with uveitis who has juvenile idiopathic arthritis. Other complications of uveitis include keratotic bands, cataracts, and vision impairment.*

Chia A, Elizabeth Graham, Clive Edelstein. Am J Ophthalmol. 2003 Jun;135(6):757-62.

Guidelines for Screening for Uveitis in Juvenile Idiopathic Arthritis (JIA)
Produced jointly by BSPAR and the RCPOphth 2006

Specific Screening Schedules

These schedules are the best recommendation possible with current data and are focused on the highest risk groups.

First screening within 6 weeks of referral
Two monthly intervals **from onset of arthritis** for 6 months
Then 3-4 monthly screening for time outlined below:

a) **Oligoarticular JIA, Psoriatic arthritis onset and Enthesitis related arthritis (ERA)** irrespective of ANA status **onset under 11 years**

Age at onset	Length of screening
<3 yrs	8 years
3-4yrs	6 yrs
5-8yrs	3 yrs
9-10yrs	1 yr

b) **Polyarticular, ANA+ JIA onset < 10 years**

AGE at onset	Length of screening
<6 yrs	5 yrs
6-9 yrs	2 yrs

c) **Polyarticular, ANA- JIA, onset <7years**
All children need 5 yrs screening

Complication #2

- Leg length discrepancy
  - Hyperemia to the juxtaposed growth plates
  - >1 cm clinically significant
  - Helped by intra-articular steroids
- Thigh circumference discrepancy
  - Disuse

Sherry DD et al. Arthritis Rheum. 1999;42(11):2330

Long-Term Outcome in Patients With Juvenile Idiopathic Arthritis

Kirsten Minden,[1] Martina Niewerth,[2] Joachim Listing,[2] Thomas Biedermann,[3] Matthias Bollow,[4] Monika Schöntube,[3] and Angela Zink[2]

- German study, 215 patients
- Patients seen 1978-88, contacted in 1998

Table 1. Patient characteristics according to diagnosis at disease onset*

Cohort	n	% female	Median age at onset (range)	Median age at followup (range)
Whole				
Systemic arthritis	30	47	4 (0–15)	20 (14–31)
Oligoarthritis	85	60	4 (1–14)	21 (14–34)
Polyarthritis				
RF+	3	100	12 (12–13)	29 (24–32)
RF−	27	85	7 (1–13)	22 (14–36)
Psoriatic arthritis	3	33	12 (12–15)	30 (24–31)
Enthesitis-related arthritis	33	24	11 (4–15)	25 (17–35)
Other arthritis	34	49	8 (1–15)	25 (15–34)
Total	215	54	6 (0–15)	23 (14–36)
Population-based				
Systemic arthritis	5	60	4 (2–7)	20 (17–24)
Oligoarthritis	29	59	5 (1–13)	21 (14–32)
Polyarthritis				
RF+	1	100	12	29
RF−	9	78	7 (1–12)	22 (17–28)
Psoriatic arthritis	1	0	15	30
Enthesitis-related arthritis	12	17	9 (5–14)	25 (17–35)
Other arthritis	17	41	8 (2–14)	25 (16–33)
Total	74	50	7 (1–15)	22 (14–35)

Minden K et al. Arthritis Rheum. 2002;46(9):2392

Long-Term Outcome in Patients With Juvenile Idiopathic Arthritis

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- 45% underwent synovectomy
- 4 hips, 1 knee replaced
- Remission
  - 73% persistent oligo
  - 12% extended oligo
  - 0% in RF + poly

Table 4. No. (%) of patients with partial or complete remission at followup*

	Whole cohort (n = 215)		Population-based cohort (n = 74)	
	Partial	Complete	Partial	Complete
Systemic arthritis	2 (7)	14 (47)	1 (20)	3 (60)
Oligoarthritis	4 (5)	46 (54)	3 (10)	14 (48)
Polyarthritis				
RF+	0	0	0	0
RF−	3 (11)	8 (30)	3 (33)	2 (22)
Psoriatic arthritis	0	1 (33)	0	0
Enthesitis-related arthritis	1 (3)	6 (18)	0	2 (17)
Other arthritis	0	12 (35)	0	6 (35)
Total	10 (5)	87 (40)	7 (9)	27 (36)

* RF = rheumatoid factor.

Minden K et al. Arthritis Rheum. 2002;46(9):2392

Long-Term Outcome in Patients With Juvenile Idiopathic Arthritis

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Table 5. Disease activity, pain, morning stiffness, and antirheumatic treatment at followup*

Patient group	Disease activity	Pain	Morning stiffness	Antirheumatic treatment	
				NSAIDs	DMARDs
Systemic arthritis	13 (45)	15 (52)	9 (30)	6 (20)	12 (40)
Oligoarthritis	41 (48)	44 (52)	24 (28)	15 (18)	18 (21)
Polyarthritis					
RF+	3 (100)	3 (100)	2 (67)	2 (67)	2 (67)
RF−	19 (70)	17 (63)	14 (52)	4 (15)	7 (26)
Psoriatic arthritis	2 (67)	2 (67)	0	1 (33)	1 (33)
ERA	18 (56)	20 (63)	17 (52)	9 (27)	9 (27)
Other	17 (50)	15 (44)	14 (41)	8 (24)	6 (18)
Total	113 (53)	116 (55)	80 (37)	45 (21)	55 (26)

* Values are the no. (%). Patients included are those who assessed disease activity or pain >0 on an 11-point numeric rating scale (range 0–10) or reported having had morning stiffness within the 7 days prior to the assessment. NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs; RF = rheumatoid factor; ERA = enthesitis-related arthritis.

Minden K et al. Arthritis Rheum. 2002;46(9):2392

Long-Term Outcome in Patients With Juvenile Idiopathic Arthritis

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Organ complications

- Eye – 14% had uveitis, 7% with sequelae
- Heart – 5% pericarditis/myocarditis

Local growth abnormalities

- Leg-length discrepancy – 24%, mean 1cm
- Micrognathia – 9.5%

Other

- Mortality – 0%
- Amyloidosis – 1.4%
- Malignancy – 1%

Minden K et al. Arthritis Rheum. 2002;46(9):2392

Long-Term Outcome in Patients With Juvenile Idiopathic Arthritis

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Mobility

- 13% need daily assistance

Education

- Better than national average

Employment

- 5% unable to work

Living

- 18% with parents, 28% alone, 52% with partner
- 59% felt physically burdened
- 37% felt emotionally burdened

Minden K et al. Arthritis Rheum. 2002;46(9):2392

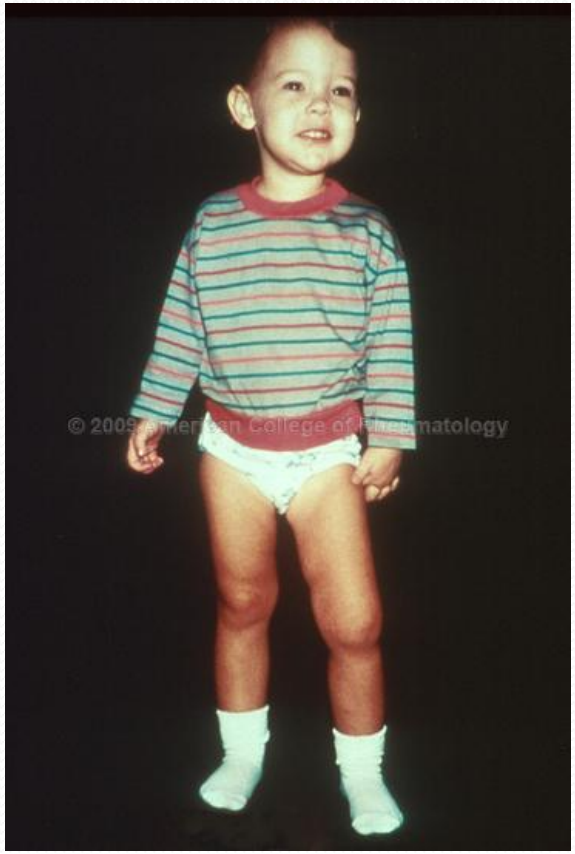
Oligoarthritis

- Arthritis affecting one to 4 joints during the first 6 months of disease.
- Two subcategories:
  - Persistent oligoarthritis: Affecting not more than 4 joints throughout the disease course
  - Extended oligoarthritis: Affecting a total of more than 4 joints after the first 6 months of disease

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

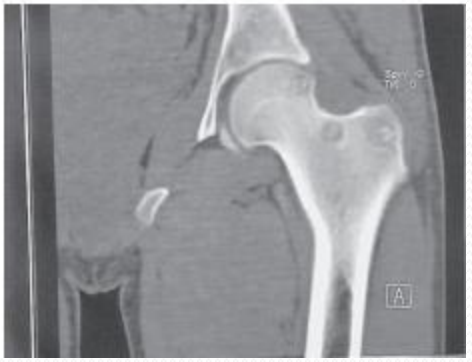
Oligoarthritis – Typical patient

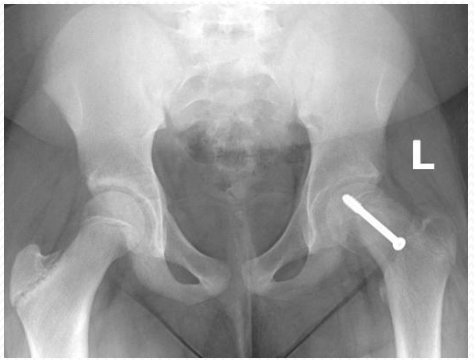
- Girl aged 4
- Family notices she “walks funny” in the mornings
- Girl doesn’t complain
- Then the knee swells up (typically knee/ankle/wrist/elbow)
- ANA positive
- ESR/CRP normal



Oligoarthritis

- Differential diagnosis
  - Dactylitis – psoriatic arthritis
  - Enthesitis related arthritis – typically if age>9
  - Rarely
    - Plant thorn synovitis
    - Septic arthritis
    - Osteoarthritis
    - Lyme disease
  - Neoplastic
    - ALL, neuroblastoma – more pain, sicker (x-ray)
  - Hip first
    - Toxic synovitis (age 3-10, M>F, aka transient synovitis)
    - Legg-Calves-Perthes (age 5-12)
    - Slipped capital femoral epiphysis (age 7-11)
    - Osteoid osteoma (age 4-25)





Extended oligoarthritis

- Progression to polyarticular disease
  - 205 patients
  - 10 years f/u
    - 40% extended to >4 joints
    - 18% to >10 joints
  - Predictors
    - Anaemia, high ESR, symmetry, ankle and wrist
  - Likely to persistent into adulthood

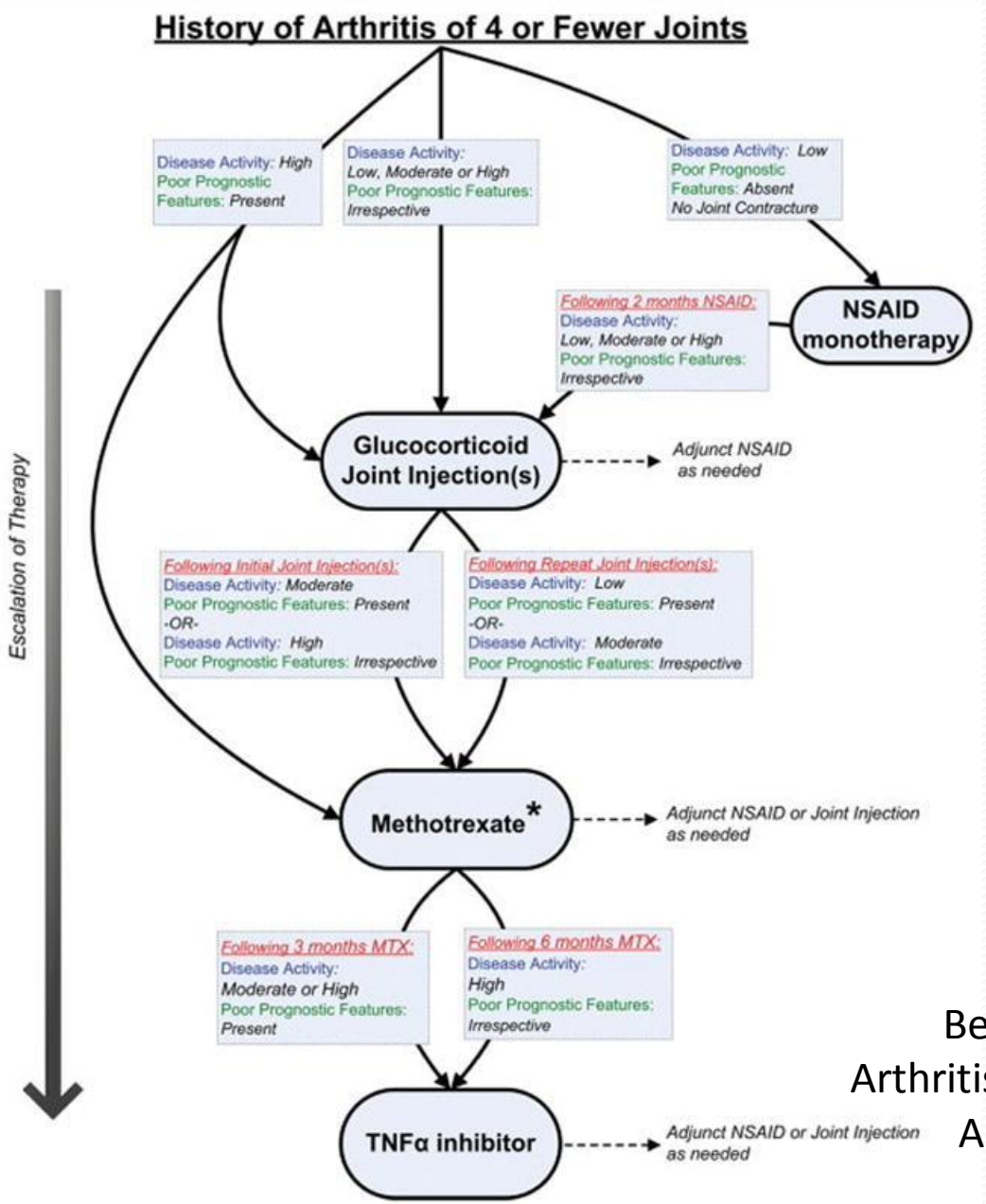
Outcome	Predictor variables (confounder)†	Analysis 1‡		
		n	OR (95% CI)	*P*
Polyarticular course (≥10 joints)	Symmetry	142	19.2 (5.46–67.8)	0.000
	Ankle and/or wrist disease		6.61 (1.97–22.1)	0.002
	ESR ≥20 mm/hour		3.76 (1.09–12.9)	0.036
	Wrist disease		E	
	(Disease duration)		1.18 (1.03–1.34)	0.018
DMARD use	Symmetry	142	11.5 (4.22–31.3)	0.000
	Wrist disease		5.87 (1.51–22.8)	0.010
	ESR ≥20 mm/hour		6.47 (2.2–18.9)	0.001
	Ankle and/or wrist disease		E	
	(Disease duration)		E	
Erosive disease	Symmetry	83	4.73 (1.47–15.2)	0.009
	Ankle and/or wrist disease		3.59 (1.15–11.2)	0.027
	(Disease duration)		1.19 (1.05–1.37)	0.007
PGA ≥1 at last followup visit	Symmetry	135	3.23 (1.45–7.2)	0.028
	Wrist disease		4.01 (1.16–13.8)	0.004
No remissions	Symmetry	142	4.73 (2.15–10.4)	0.000
	ESR ≥20 mm/hour		2.30 (1.04–5.08)	0.039
Disability (C-HAQ score >0.12)	Symmetry	72	2.95 (1.01–8.6)	0.048

Al-Matar MJ et al. Arthritis Rheum. 2002;46(10):2708.

History of arthritis of four or fewer joints

- This group includes patients with the ILAR categories of
  - persistent oligoarthritis, as well as patients with
  - psoriatic arthritis
  - enthesitis-related arthritis, and
  - undifferentiated arthritis
- who have developed active arthritis in only four or fewer joints total throughout the history of their disease course.

Beukelman T et al. Arthritis Care Res. 2011 Apr;63(4):465-82.



Beukelman T et al.
Arthritis Care Res. 2011
Apr;63(4):465-82.

Polyarthritis (RF negative)

- Arthritis affecting 5 or more joints during the first 6 months of disease
- a test for RF is negative

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

Polyarthritis (RF positive)

- Arthritis affecting 5 or more joints during the first 6 months of disease
- 2 or more tests for RF at least 3 months apart during the first 6 months of disease are positive.

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

Polyarthritis – Typical patient

Young onset: age 2-5

- Indolent onset
- Starts with 1-2 joints, progress to >4 joints in <6/12
- Symmetrical: knees, wrists, and ankles most frequently
- Risk of uveitis (<oligo), esp. if ANA +ve
- Often ANA +ve
- All RF negative (consider alternative diagnosis if +ve)

Older onset: age 10-14

- Relatively rapid onset
- Multiple joints
- Fingers, wrists, elbows, the cervical spine, hips, knees, and ankles
- Pain often initially out of proportion to inflammation and stiffness
- RF +ve – similar to adult RA
- RF –ve – a different disease!

ESR, anaemia, hypergammaglobulinaemia

Polyarthritis – differential diagnosis

- serum sickness, viral infections, and many other forms of reactive arthritis
- early onset psoriatic arthritis (skin, FHx, assymetry)
- early onset spondyloarthropathy (FHx, assymetry, enthesitis)
- SLE (ENAs, skin)
- Systemic vasculitis (ANCA, kidney, skin)
- Sarcoidosis (Ca++, CXR, posterior uveitis, destructive arthritis)
- Inflammatory Bowel Disease (abdominal pain)
- Epiphyseal dysplasia (x-ray, rare progressive pseudorheumatoid arthropathy of childhood)
- Minocycline-induced autoimmunity (acne!)

History of arthritis of five or more joints

- This group includes patients with the ILAR categories of
  - extended oligoarthritis
  - RF negative polyarthritis
  - RF positive polyarthritis, as well as patients with
  - psoriatic arthritis
  - enthesitis-related arthritis, and
  - undifferentiated arthritis
- who have developed active arthritis in five or more joints total throughout the history of their disease.
- Patients in this group need not currently have five or more active joints.

Beukelman T et al. Arthritis Care Res. 2011 Apr;63(4):465-82.

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PENICILLAMINE AND HYDROXYCHLOROQUINE IN THE TREATMENT OF SEVERE JUVENILE RHEUMATOID ARTHRITIS

Results of the U.S.A.–U.S.S.R. Double-Blind Placebo-Controlled Trial

EARL J. BREWER, M.D., EDWARD H. GIANNINI, DR.P.H., NINA KUZMINA, M.D., AND LEV ALEKSEEV, M.D.

Table 1. Selected Indexes of Articular Disease and Hematologic Features in 162 Children with Rheumatoid Arthritis, According to Treatment Group.*

INDEX	PENICILLAMINE (N = 54)	HYDROXY-CHLOROQUINE (N = 57)	PLACEBO (N = 51)
No. of joints with swelling	15.5±11.9	15.3±11.6	14.4±9.3
Severity of joint swelling†	22.4±18.4	19.9±16.7	18.1±12.2
No. of joints with pain upon movement	10.1±13.5	11.2±11.5	7.5±8.4
Severity of pain upon movement†	15.1±21.9	13.8±13.9	9.5±11.3
No. of joints with limitation of movement	15.3±13.7	14.9±13.8	11.5±10.4
Severity of limitation of movement†	23.2±25.3	21.3±23.7	15±10.4
No. of joints with active arthritis	18±13.5	18.6±13.1	16.3±10.6
Total sum of severity†	76.4±79.7	65.0±53.5	52.2±38.2
Duration of morning stiffness (min)	64.3±100.2	35.6±39.2	51.7±114.6
Erythrocyte sedimentation rate (mm/hr)	32±23	28±23	30±21
Hematocrit (percent)	34.7	34.3	35
White-cell count	7,600	7,600	8,100
Platelet count	347,000	358,000	345,000

N Engl J Med. 1986; 314(20):1269-76.

Methotrexate USA-USSR trial

- 127 children
- Randomised: 10 mg MTX/m^2, 5 mg MTX/m^2, or placebo for six months
- Mean age 10.1 years
- Mean duration 5.1 years

Table 1. Demographic and Clinical Characteristics of the Patients at Entry, According to Study Group.

Characteristic*	Low-Dose Methotrexate (N = 46)	Very-Low-Dose Methotrexate (N = 40)	Placebo (N = 41)
Age (yr)			
Average	10.1	9.6	10.6
Range	2.5–17.5	3.3–17.4	3.2–17.8
Disease duration (yr)			
Average	4.8	4.8	5.8
Range	0.6–13.5	0.5–11.8	0.5–14.4
No. (%) female	33 (72)	29 (73)	34 (83)
No. (%) taking low-dose prednisone	15 (33)	15 (37)	14 (34)
No. (%) taking two NSAIDs†	5 (11)	3 (7.5)	3 (7.3)
No. (%) with systemic-onset disease	9 (20)	11 (28)	12 (29)
Mean (±SE) no. of joints with active arthritis‡	27 (2)	21 (2)	24 (2)

*There were no significant differences among the treatment groups in any of the characteristics.

Giannini EH et al. N Engl J Med. 1992 Apr 16;326(16):1043-9.

Methotrexate USA-USSR trial

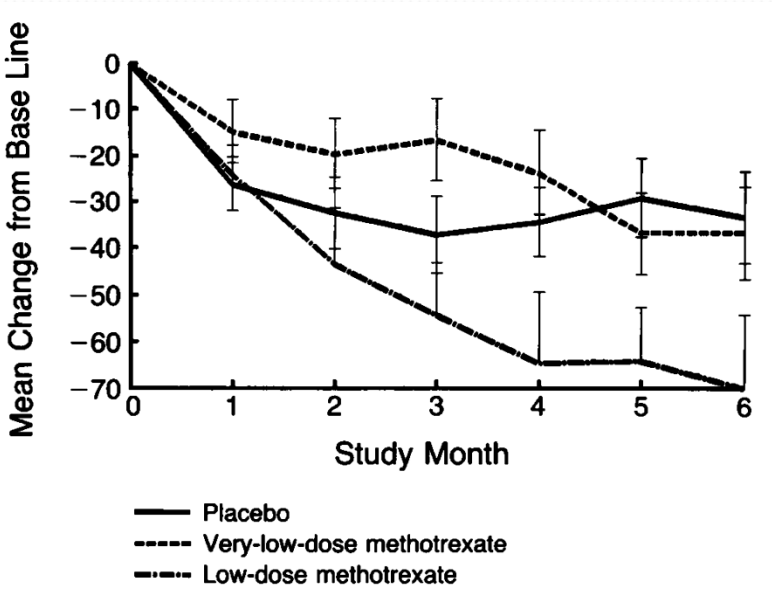


Figure 2. Mean (±SE) Change from Base Line in the Articular-Severity Score.

The articular-severity score was defined as the sum of the severity scores for swelling, pain on motion, tenderness, and limitation of motion, calculated for each joint and then totaled.

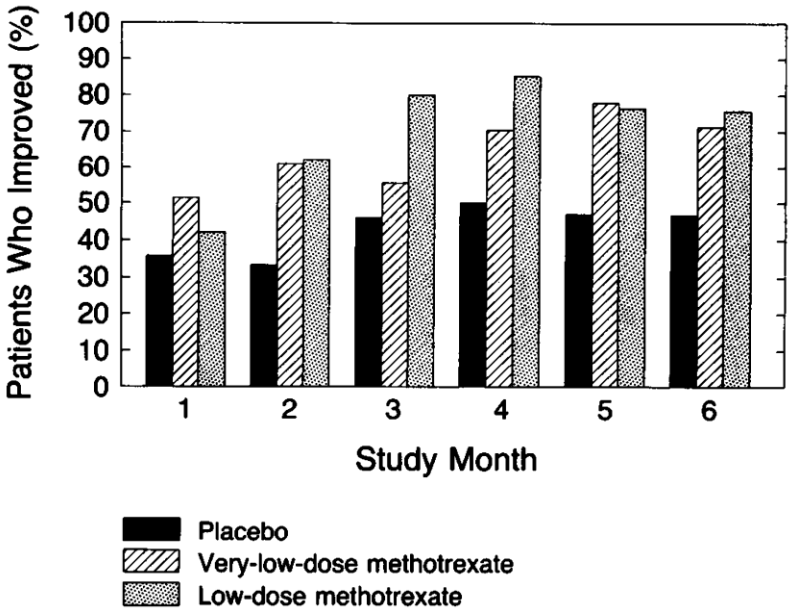


Figure 1. Physicians' Global Assessment of Patients' Response to Therapy.

Giannini EH et al. N Engl J Med. 1992 Apr 16;326(16):1043-9.

Methotrexate USA-USSR trial

Table 2. Changes in the Indexes of Articular Disease at the Final Visit, According to Study Group.

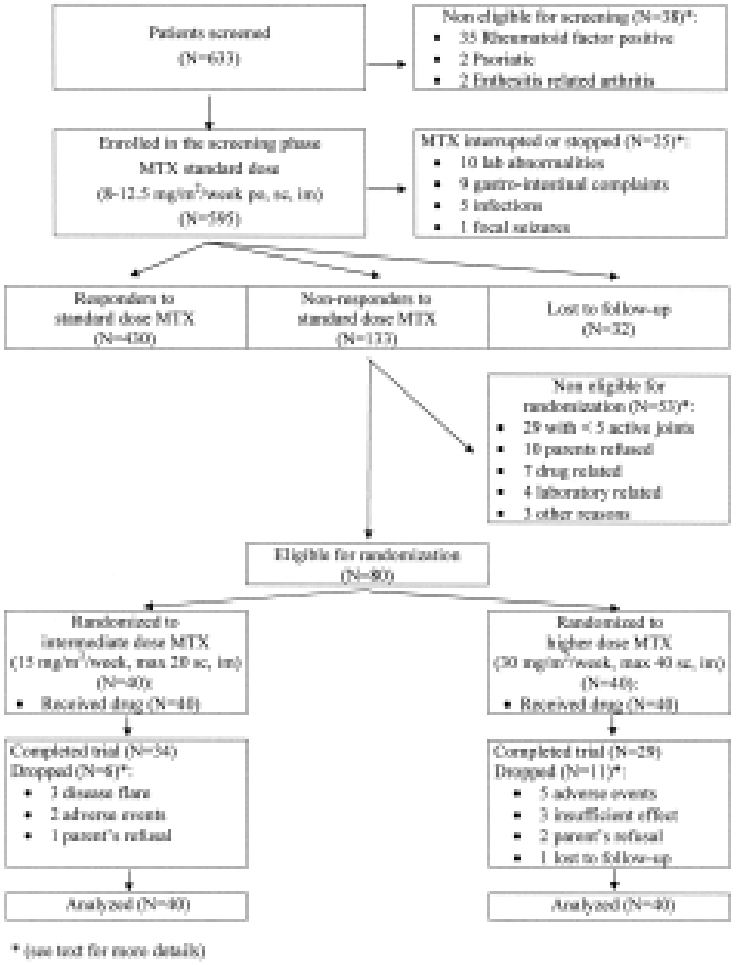
Index	Low-Dose Methotrexate (N = 38)	Very-Low-Dose Methotrexate (N = 37)	Placebo (N = 39)	P Value*
		mean (±SE) and median changes from base line		
No. of joints with swelling	−7.1±1.8, −5.5	−4.9±1.7, −2	−4.3±1.4, −4	>0.3
Severity of swelling	−14.5±3.3, −10	−9.3±2.6, −4	−9.2±2.3, −8	>0.3
No. of joints with pain on motion	−11.0±2.2, −5	−3.0±1.7, −1	−7.1±2.1, −3	0.016
Severity of pain on motion	−19.0±4.4, −10	−6.1±2.5, −2	−11.5±3.1, −5	0.02
No. of joints with tenderness	−9.0±2.1, −6.5	−4.9±1.7, −2	−5.2±2.1, −2	0.257
Severity of tenderness	−17.1±4.6, −9	−7.7±2.4, −4	−9.0±2.7, −4	0.109
No. of joints with limitation of motion	−5.4±1.7, −3.5	−0.5±1.6, 0	−0.7±1.3, −1	0.04
Severity of limitation of motion	−12.2±4.4, −10	−5.0±2.9, −6	−4.1±2.4, −3	0.166
No. of joints with active arthritis	−7.5±2.6, −7	−5.2±2.0, −1	−5.2±1.5, −4	>0.3
Articular-severity score	−63.0±15.0, −52	−28.0±9.0, −17	−36.4±8.8, −24	0.077
Duration of morning stiffness (min)	−52.3±11.8, −30	−50.5±22.9, −18.5	−41.8±15.1, −20	>0.3

*By unadjusted analysis of variance.

Giannini EH et al. N Engl J Med. 1992 Apr 16;326(16):1043-9.

MTX dose RCT

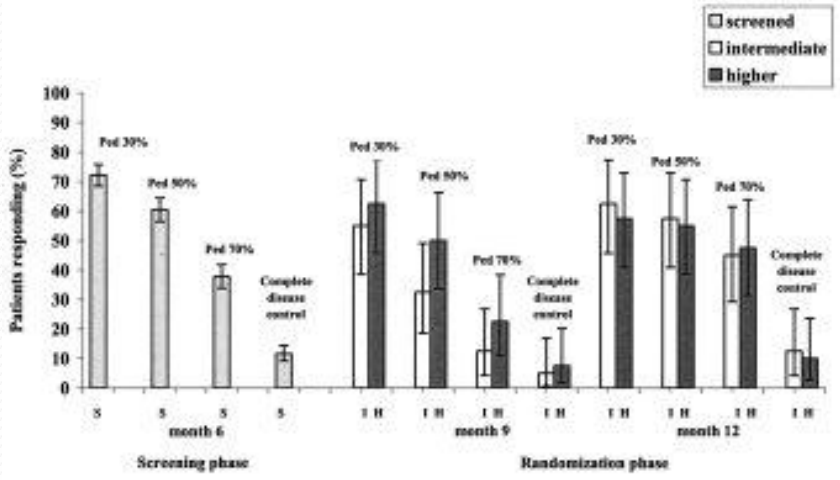
- Patients with polyarticular-course juvenile idiopathic arthritis who failed (<ACR Pedi 30 response) standard dose MTX (8-12.5 mg/m^2/week):
- Randomised to:
  - intermediate dosage (15 mg/m^2/week) vs
  - a higher dosage (30 mg/m^2/week)



Ruperto N et al. Arthritis Rheum. 2004 Jul;50(7):2191-201.

MTX dose RCT

- 28% failed standard MTX
- 80 randomised:
  - ACR 30 response
    - 63% vs 58% (inter vs high)
  - ACR 50 response
    - 58% vs 55% (inter vs high)
  - ACR 70 response
    - 45% vs 48% (inter vs high)
- No difference in AEs



Ruperto N et al. Arthritis Rheum. 2004 Jul;50(7):2191-201.

Etanercept RCT

- 4-17 year of age
- Background of pauciarthritis, polyarthritis or systemic
- “Active” polyarticular disease
  - five or more swollen joints
  - three or more joints with limitation of motion and pain, tenderness, or both
- DMARDs washed out (MTX 14/7, others 28/7)
- 3 month open label run-in
- Responders randomised to etanercept or placebo, for 4 months or until disease flare
- Primary outcome: number of patients with disease flare

Lovell DJ et al. N Engl J Med. 2000 Mar 16;342(11):763-9.

Etanercept RCT

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND DISEASE HISTORY.*

CHARACTERISTIC	OPEN-LABEL STUDY (N=69)	DOUBLE-BLIND STUDY		
		TOTAL (N=51)	PLACEBO (N=26)	ETANERCEPT (N=25)
Mean age — yr	10.5	10.6	12.2	8.9
Age group — no. (%)				
4–8 yr	25 (36)	18 (35)	5 (19)	13 (52)
9–12 yr	14 (20)	9 (18)	4 (15)	5 (20)
13–17 yr	30 (43)	24 (47)	17 (65)	7 (28)
Sex — no. (%)				
Female	43 (62)	34 (67)	15 (58)	19 (76)
Male	26 (38)	17 (33)	11 (42)	6 (24)
Race or ethnic group — no. (%)				
White	52 (75)	37 (73)	23 (88)	14 (56)
Black	6 (9)	4 (8)	1 (4)	3 (12)
Hispanic	9 (13)	8 (16)	2 (8)	6 (24)
Other	2 (3)	2 (4)	0	2 (8)
Type of onset of JRA — no. (%)				
Pauciarticular	7 (10)	3 (6)	1 (4)	2 (8)
Polyarticular	40 (58)	31 (61)	17 (65)	14 (56)
Systemic	22 (32)	17 (33)	8 (31)	9 (36)
Mean duration of JRA — yr	5.9	5.8	6.4	5.3
Positive for rheumatoid factor — no. (%)	15 (22)	12 (24)	8 (31)	4 (16)
Previous methotrexate therapy — no. (%)	69 (100)	51 (100)	26 (100)	25 (100)
DMARDs at washout — no. (%)	51 (74)	35 (69)	19 (73)	16 (64)
Methotrexate	50 (72)	34 (67)	18 (69)	16 (64)
Hydroxychloroquine	13 (19)	9 (18)	7 (27)	2 (8)
Concomitant therapy at washout — no. (%)				
Corticosteroids	25 (36)	19 (37)	13 (50)	6 (24)
NSAIDs	66 (96)	49 (96)	24 (92)	25 (100)
Mean dose of corticosteroids — mg/day	5.6	5.8	5.5	6.5

Lovell DJ et al. N Engl J Med. 2000 Mar 16;342(11):763-9.

Etanercept RCT

TABLE 2. MEASURES OF DISEASE ACTIVITY AND IMPROVEMENT FROM BASE LINE.*

MEASURE	OPEN-LABEL STUDY (N=69)					DOUBLE-BLIND STUDY, PLACEBO (N=26)			DOUBLE-BLIND STUDY, ETANERCEPT (N=25)		
	BASE LINE	MO 1	MO 2	MO 3	% IMPROVEMENT†	BASE LINE	MO 3	MO 7	BASE LINE	MO 3	MO 7
Juvenile rheumatoid arthritis core set criteria											
Total no. of active joints‡	28	22	15	13	56	27.0	7.5	13.0	32.0	13.0	7.0
No. of joints with limitation of motion and with pain, tenderness, or both‡	10	4	3	2	79	6.5	1.0	4.5	8.0	2.0	1.0
Physician's global assessment of disease severity§	7	3	3	2	60	6	1	5	7	2	2
Patient's or parent's global assessment of overall well-being§	5	3	3	2	50	5	1	5	5	2	3
Score on Childhood Health Assessment Questionnaire¶	1.4	1.0	0.9	0.9	37	1.3	0.4	1.2	1.6	0.9	0.8
Erythrocyte sedimentation rate‖	35	18	20	20	50	27	12	30	41	15	18
Additional assessments											
Articular severity score**	88	60	47	45	50	84	36	66	90	35	38
Duration of stiffness (min)	45	15	15	15	75	60	5	38	45	15	5
Pain (on a visual-analogue scale)††	3.6	2.1	1.3	1.4	63	3.5	0.3	3.5	3.5	1.3	1.5
C-reactive protein (mg/dl)‡‡	3.5	0.9	1.1	0.8	60	1.8	0.3	3.0	3.5	0.2	0.4
Other‡											
No. of swollen joints	25	16	11	9	58	22.5	6.0	11.0	27.0	12.0	4.0
No. of joints with limitation of motion	23	20	18	15	23	23	17	22	24	12	9

Lovell DJ et al. N Engl J Med. 2000 Mar 16;342(11):763-9.

Etanercept RCT

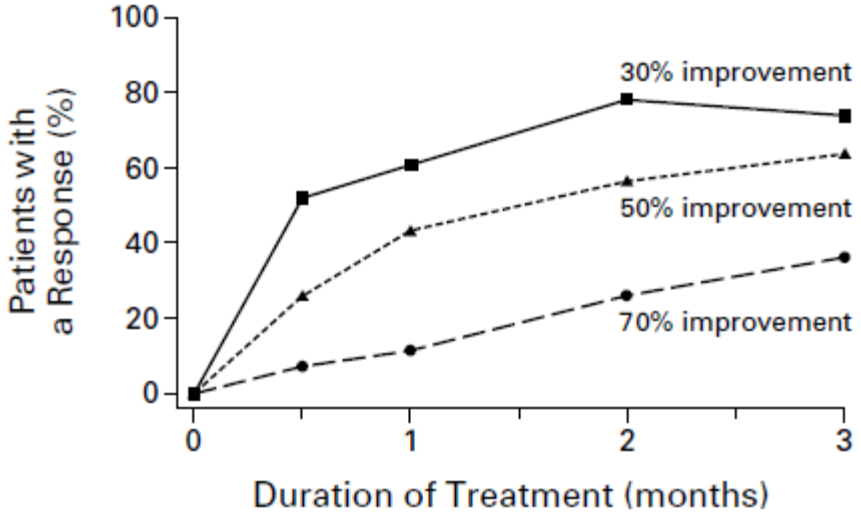


Figure 1. Incidence of 30, 50, and 70 Percent Improvement in the 69 Patients Who Received Etanercept in the Open-Label Study.

At the end of the open-label study, 51 (74 percent) of the patients had a 30 percent improvement, 44 (64 percent) had a 50 percent improvement, and 25 (36 percent) had a 70 percent improvement, as compared with base line.

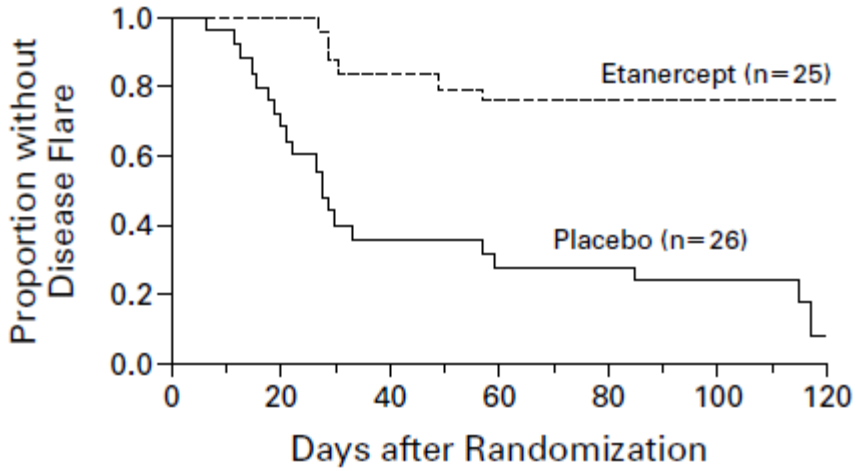


Figure 2. Kaplan–Meier Analysis of the Time to Disease Flare.

The median time to disease flare was significantly shorter among the patients who received placebo (28 days) than among those who received etanercept (>116 days, $P<0.001$) in the double-blind study.

Lovell DJ et al. N Engl J Med. 2000 Mar 16;342(11):763-9.

Etanercept RCT

- Etanercept alone

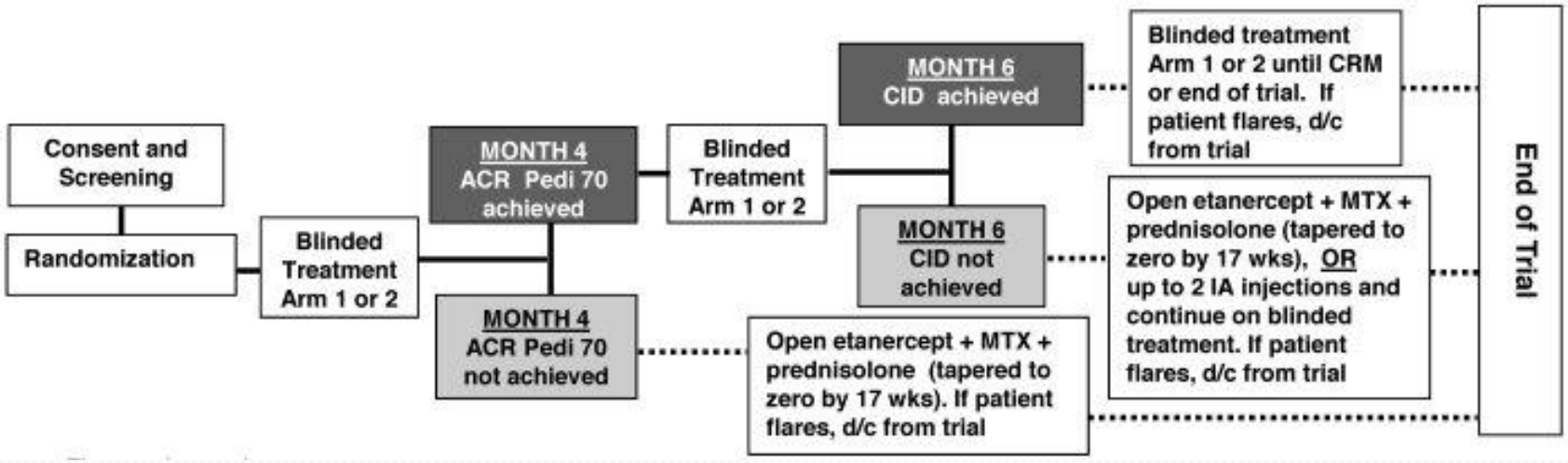
TABLE 3. INCIDENCE OF DISEASE FLARE IN THE DOUBLE-BLIND STUDY ACCORDING TO THE BASE-LINE CHARACTERISTICS OF THE PATIENTS.

VARIABLE*	PLACEBO	ETANERCEPT
	no./total no. (%)	
Total with disease flare	21/26 (81)	7/25 (28)
Age group		
4–8 yr	4/5 (80)	3/13 (23)
9–12 yr	4/4 (100)	1/5 (20)
13–17 yr	13/17 (76)	3/7 (43)
Sex		
Female	14/15 (93)	5/19 (26)
Male	7/11 (64)	2/6 (33)
Race or ethnic group		
White	18/23 (78)	4/14 (29)
Black	1/1 (100)	1/3 (33)
Hispanic	2/2 (100)	1/6 (17)
Other	0	1/2 (50)
Rheumatoid factor		
Positive	8/8 (100)	0/4 (0)
Negative	13/18 (72)	7/21 (33)
Type of juvenile rheumatoid arthritis at onset		
Pauciarticular	1/1 (100)	0/2 (0)
Polyarticular	13/17 (76)	3/14 (21)
Systemic	7/8 (88)	4/9 (44)
Corticosteroid use at base line†		
Yes	12/13 (92)	3/6 (50)
No	9/13 (69)	4/19 (21)

Lovell DJ et al. N Engl J Med. 2000 Mar 16;342(11):763-9.

Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis

- Age 2-16 with active juvenile polyarthritis <12 months
- Treatment naïve (MTX<6/52 allowed)
- Randomised to MTX or MTX + Pred + Etanercept
- Primary outcome: clinical inactive disease at 6 months



Wallace CA et al. Arthritis Rheum. 2012 Jun;64(6):2012-2021.

Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis

- Mean age 10 years
- Mean duration 5 months
- Active disease
  - Physician's assessment 7/10
- 1/3 positive for RF/CCP

	Arm 1 (n = 42)	Arm 2 (n = 43)
Sex, no. (%)		
Female	29 (69.0)	34 (79.1)
Male	13 (31.0)	9 (20.9)
Race, no. (%)		
White	35 (83.3)	38 (88.4)
Black	4 (9.5)	1 (2.3)
Other	3 (7.1)	4 (9.3)
Age at baseline, years	9.9 ± 4.6	11.1 ± 4.1
Duration of symptoms, months	4.9 ± 0.5	5.2 ± 0.6
No. of joints with active disease	18.3 ± 11.0	25.5 ± 14.4†
No. of joints with limited motion	13.6 ± 11.8	16.3 ± 13.2
C-HAQ disability index score	1.1 ± 0.8	1.3 ± 0.7
Parent's assessment of well-being	5.6 ± 2.1	5.2 ± 2.8
Physician's assessment of disease activity	7.0 ± 1.8	7.1 ± 1.9
ESR, mm/hour	29.0 ± 21	44.6 ± 30‡
Elevated ESR, no. (%)	20 (47.6)	27 (62.8)
Positive for RF, no. (%)	14 (33.3)	17 (39.5)
Positive for ANAs, no. (%)	33 (78.5)	25 (59.5)§
Positive for anti-CCP, no. (%)	14 (35)¶	16 (39)¶
Previous treatment with MTX, no. (%)	6 (14.2)	4 (9.3)
Previous treatment with prednisolone, no. (%)	2 (4.7)	2 (4.6)

Wallace CA et al. Arthritis Rheum. 2012 Jun;64(6):2012-2021.

Results

- Clinical inactive disease was induced in
  - 32% of patients by 6/12
  - in 66% by 1 year
- Primary outcome not met
  - 40% vs 23%, p=0.088
- At 12 months:
  - 21% vs 7%, p=0.053
- RF and CCP status did not predict outcome

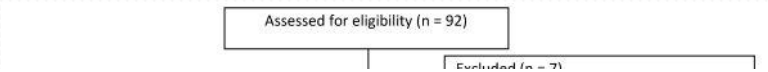
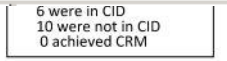


Table 2. Summary of outcomes by treatment arm*

	Arm 1 (n = 42)	Arm 2 (n = 43)	χ^2	*P*
Month 4				
Met ACR Pedi 70	30 (71)	19 (44)	6.46	0.011
Did not meet ACR Pedi 70	12 (28)	24 (55)		
Month 6				
Clinical inactive disease achieved	17 (40)	10 (23)	2.91	0.088
Clinical inactive disease not achieved	25 (60)	33 (77)		
Month 12/end of study				
Clinical remission on medication achieved	9 (21)	3 (7)	–	0.053†
Clinical remission on medication not achieved	33 (79)	40 (93)		

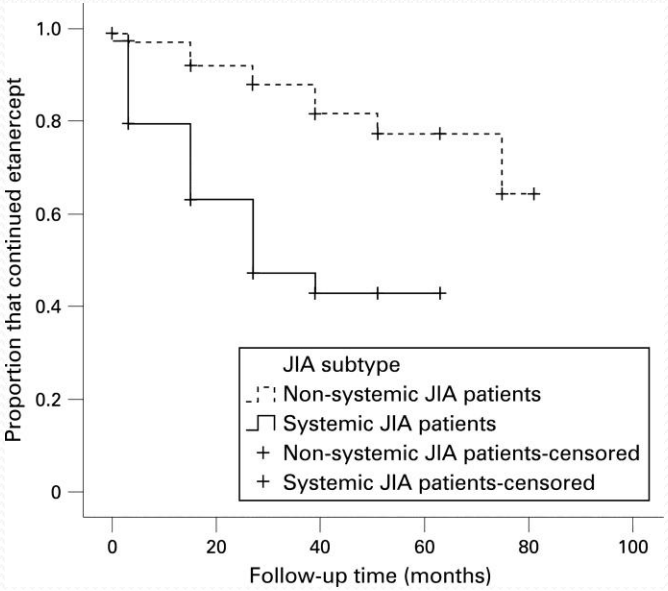
* Values are the number (%) of patients. Patients in arm 1 were treated with methotrexate (MTX), etanercept, and prednisolone. Patients in arm 2 were treated with MTX only. Outcomes were determined using the last observation carried forward method in an intent-to-treat analysis. The primary outcome measure for the trial was clinical inactive disease at month 6. Clinical remission on medication

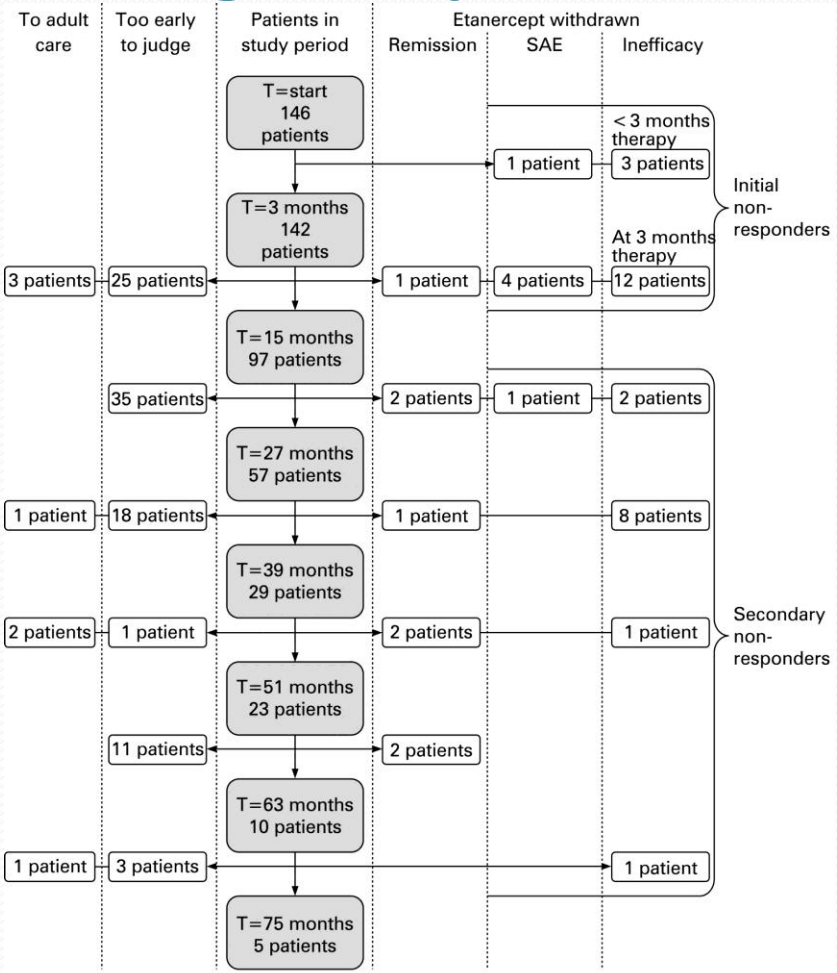


Wallace CA et al. Arthritis Rheum. 2012 Jun;64(6):2012-2021.

Etanercept Dutch Registry

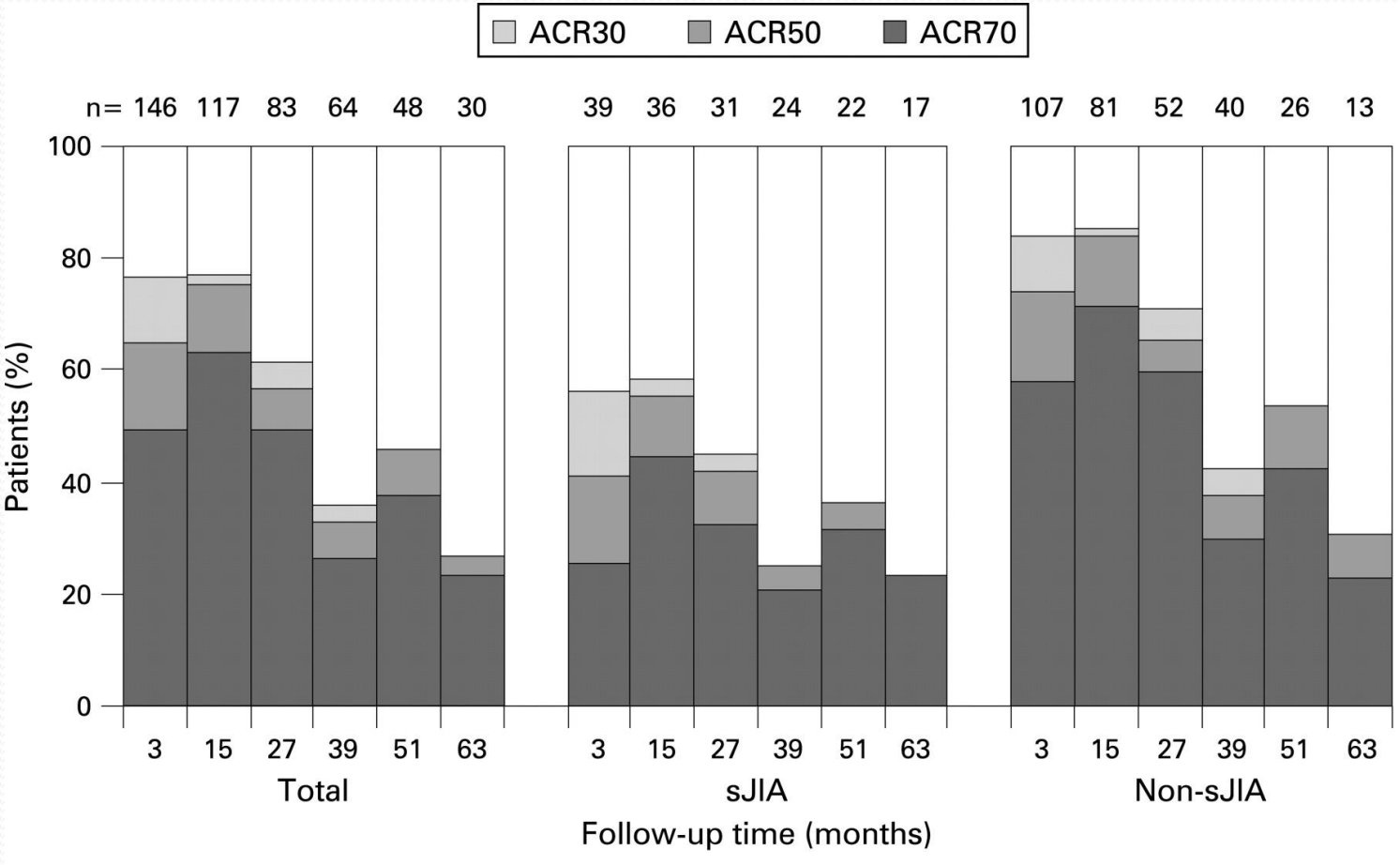
- All Dutch children given etanercept 1999-2006
- Polyarticular-course and maximal MTX insufficient





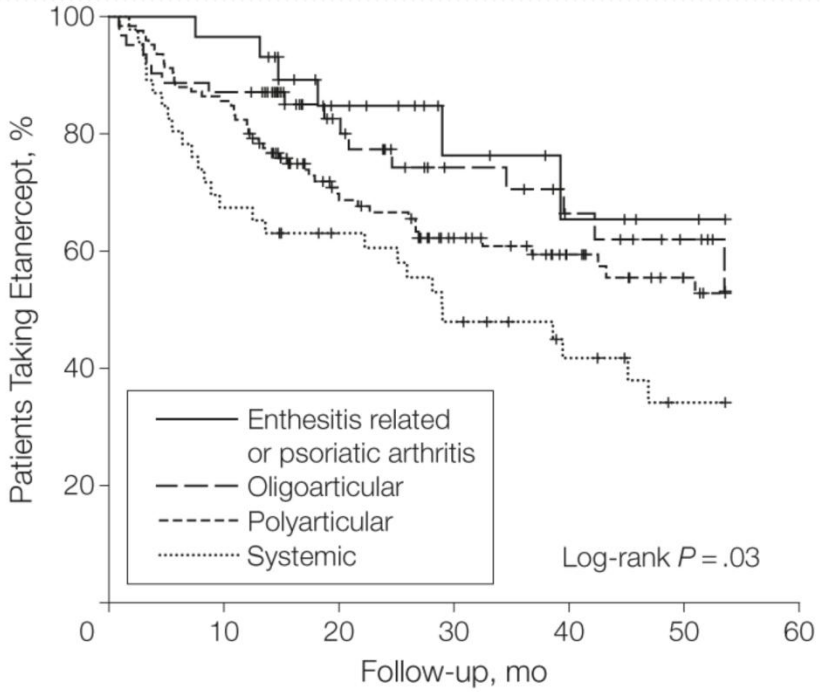
Prince F H M et al. Ann Rheum Dis 2009;68:635-641

Etanercept Dutch Registry



Prince F H M et al. Ann Rheum Dis 2009;68:635-641

Dutch Registry



No. at risk						
Enthesitis related or psoriatic arthritis	29	28	17	9	6	4
Oligoarticular JIA	62	54	32	20	15	10
Polyarticular JIA	125	107	66	48	33	21
Systemic onset JIA	46	31	25	19	13	8

Otten MH et al. JAMA. 2011;306(21):2340-2347

Dutch Registry

Table 2. Factors Associated With Response to Etanercept

Variable	Absolute Risk, %[a]		Excellent vs Intermediate and Poor Responders			
			Univariable		Multivariable	
	Excellent Responders (n = 85)	Intermediate or Poor Responders (n = 177)	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Female vs male	67	72	0.78 (0.45-1.36)	.38	0.85 (0.45-1.59)	.61
Systemic-onset JIA vs nonsystemic subtypes	13	20	0.60 (0.29-1.26)	.18	0.49 (0.20-1.18)	.11
ANA positivity vs negativity	24	23	1.05 (0.57-1.95)	.87	0.73 (0.37-1.46)	.38
Age of onset JIA, per year increase in age at onset	6	7	0.94 (0.89-1.00)	.06	0.92 (0.84-0.99)	.03
Disease duration before start of etanercept, per year	10	11	1.08 (1.01-1.15)	.04	1.05 (0.96-1.15)	.26
No. of DMARDs used before start of etanercept, per DMARD used[b]	17	18	0.90 (0.64-1.25)	.52	0.64 (0.43-0.95)	.03
VAS disease activity by physician at start of etanercept, per 10-point increase	10	11	0.86 (0.67-0.97)	.02	0.89 (0.77-1.02)	.10
CHAQ score at start of etanercept, per 1-point increase	33	42	0.49 (0.34-0.71)	<.001	0.49 (0.33-0.74)	.001
ESR at start of etanercept, per 1-unit mm/h increase	3	3	0.84 (0.50-1.41)	.51	1.03 (0.57-1.85)	.92
	Poor Responders (n = 85)	Intermediate or Excellent Responders (n= 177)	Poor vs Intermediate and Excellent Responders			
			OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Female vs male	80	66	2.05 (1.11-3.80)	.02	2.16 (1.12-4.18)	.02
Systemic-onset JIA vs nonsystemic subtypes	24	15	1.79 (0.93-3.43)	.08	2.92 (1.26-6.80)	.01
ANA positivity vs negativity	25	22	1.16 (0.63-2.13)	.63	1.29 (0.66-2.52)	.47
Age of onset of JIA, per year	7	7	1.07 (1.01-1.14)	.02	1.08 (0.99-1.16)	.07
Disease duration before start of etanercept, per year[c]	11	10	0.92 (0.85-1.00)	.04	0.95 (0.87-1.05)	.31
No. of DMARDs used before start of etanercept, per DMARD used[b]	19	17	0.98 (0.70-1.36)	.89	1.21 (0.83-1.76)	.33
VAS disease activity by physician at start of etanercept, per 10-point increase	11	11	0.96 (0.85-1.09)	.14	0.95 (0.83-1.09)	.53
CHAQ score at start of etanercept, per 1-point increase	42	37	1.31 (0.93-1.85)	.13	1.47 (0.98-2.20)	.07
ESR at start of etanercept, per 1-unit mm/h increase	3	3	1.00 (1.00-1.00)	.77	0.99 (0.98-1.00)	.21

Abbreviations: ANA, antinuclear antibody; adjusted OR, adjusted odds ratio; CHAQ, child health assessment questionnaire; CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; VAS, visual analog scale.

[a] For dichotomous variables, of the poor responders, 80% were female, whereas of the intermediate and excellent responders combined 66% were female. For continuous variables, a 33% increase in excellent responders was seen for each point increase of CHAQ score, whereas a 42% increase in intermediate and poor responders combined was seen for each point increase of CHAQ score. The OR for each variable was adjusted for the effects of the other variables.

[b] Includes methotrexate.

[c] The confidence intervals in the univariable analysis were rounded from 0.923 (95% CI, 0.854-0.997).

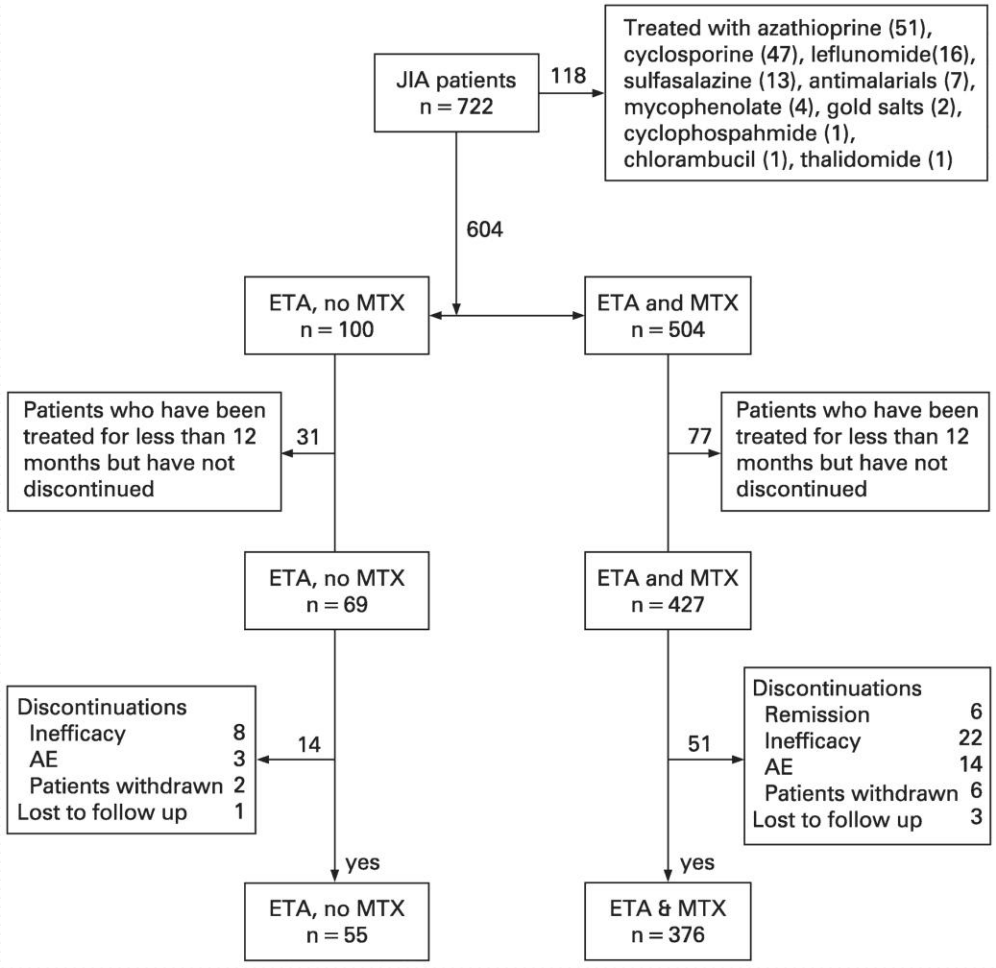
Otten MH et al. JAMA. 2011;306(21):2340-2347

Dutch Registry

- In conclusion, 15 months after initiation of etanercept:
  - one-third of the JIA patients achieved an excellent response
  - one-third an intermediate response
  - one-third a poor response.
- An excellent treatment response
  - was associated with low baseline disability scores, low number of DMARDs used before etanercept introduction, and younger age at onset of JIA
- A poor response
  - was associated with systemic JIA and female sex

Otten MH et al. JAMA. 2011;306(21):2340-2347

Germany registry data



Horneff G et al. Ann Rheum Dis. 2009 Apr;68(4):519-25.

Germany registry data

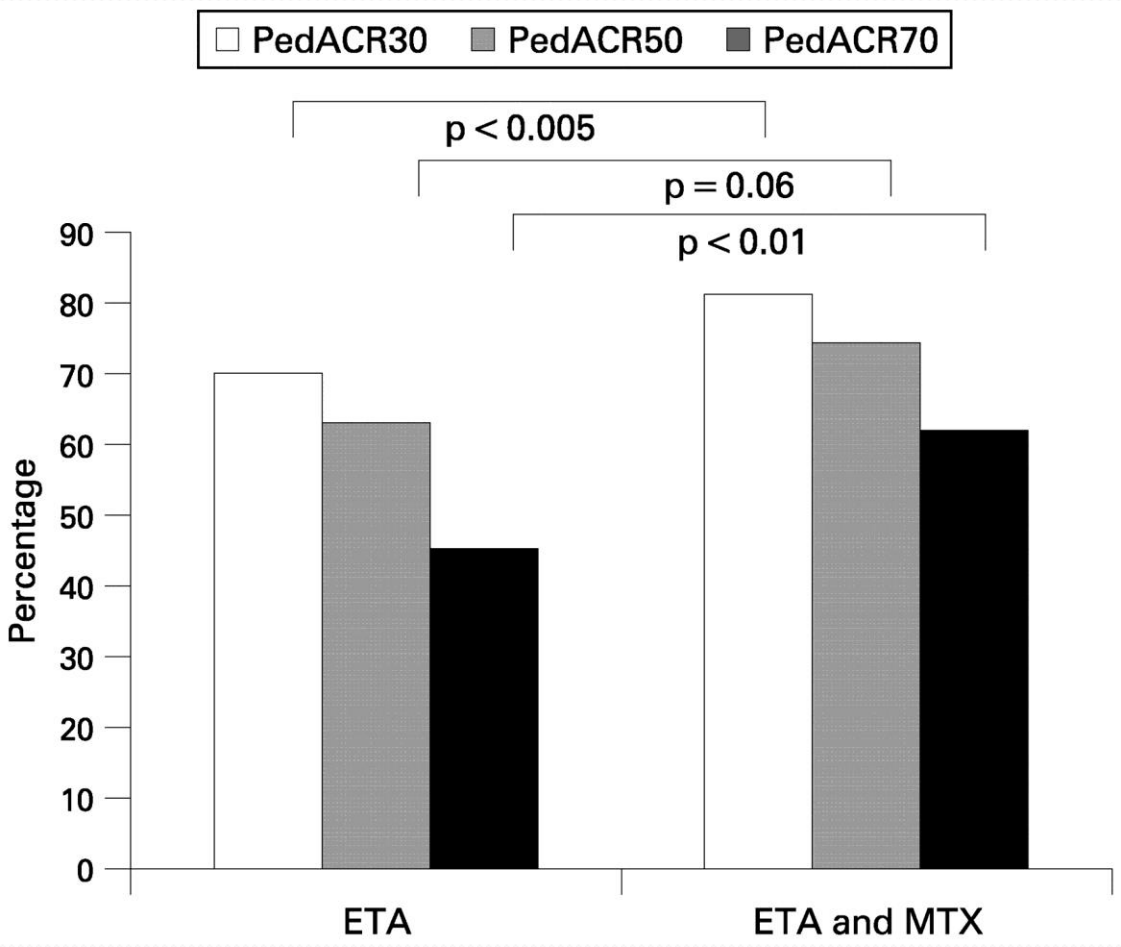
Table 1 Patient characteristics and juvenile idiopathic arthritis (JIA) subtype distribution, as per Internationa League of Associations for Rheumatology (ILAR) criteria

Diagnosis	Etanercept monotreatment (n = 100)	Etanercept and methotrexate (n = 504)
Female (%)	58 (58%)	345 (67%)
Age at disease onset, mean (SD) (median)	7.5 (4.6) (7.0)	7.6 (4.6) (7.4)
Disease duration (years), mean (SD) (median)	5.5 (4.6) (3.9)	4.9 (3.6 (3.9)
Age at start of treatment, mean (SD) (median)	13.1 (4.5) (14.9)	12.5 (4.39) (12.9)
ANA (positive/negative/unknown)	40%/47%/13%	42%/56%/2%
HLA-B27 (positive/negative/unknown)	31%/54%/15%	23%/68%/9%
Systemic arthritis (systemic onset JIA), n (%)	8 (8%)	57 (11.3%)
Seronegative polyarticular JIA. n (%)	24 (24%)	158 (31.3%)
Seropositive polyarticular JIA, n (%)	3 (3%)*	65 (12.9%)*
Persistent oligoarticular JIA, n (%)	8 (8%)	23 (4.6%)
Extended oligoarticular JIA, n (%)	17 (17%)	73 (14.5%)
Enthesitis related arthritis, n (%)	27 (27%)†	66 (13.1%)†
Psoriasis and arthritis, n (%)	7 (7%)	41 (8.1%)
Unclassified JIA, n (%)	6 (6%)	21 (4.2%)

*$p<0.01$, χ^2 test; †$p<0.001$, χ^2 test.
ANA, antinuclear antibody; HLA, human leukocyte antigen.

Horneff G et al. Ann Rheum Dis. 2009 Apr;68(4):519-25.

Germany registry data



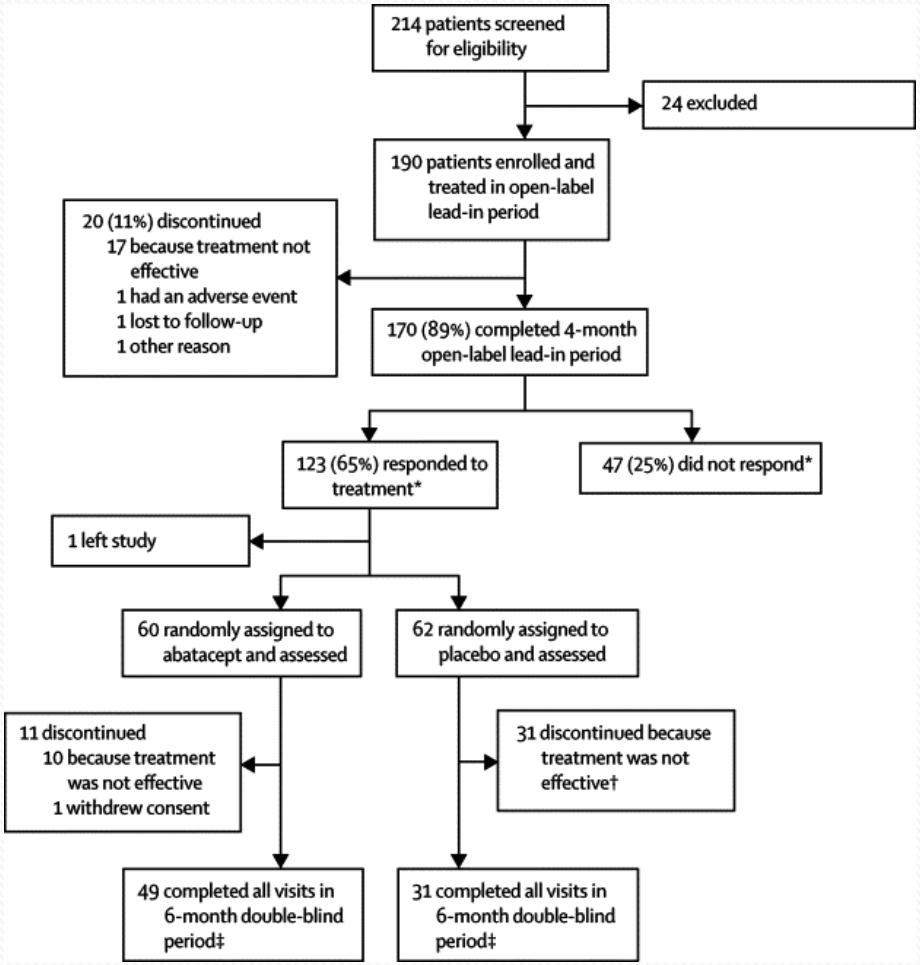
Horneff G et al. Ann Rheum Dis. 2009 Apr;68(4):519-25.

Abatacept in Polyarticular JIA

- Randomised, double-blind, placebo-controlled withdrawal trial.
- 190 patients, aged 6-17
- 45 centres
- At least 5 active joints
- Inadequate response to at least one DMARD
- Withdrawal trials
  - Recruitment easier
  - Biased towards the responders

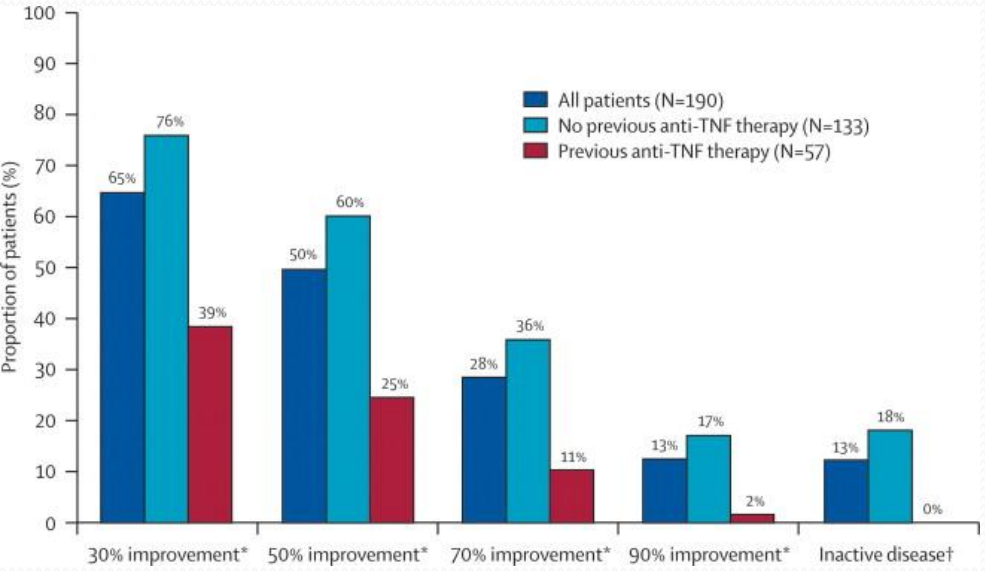
Ruperto N et al. Lancet. 2008 Aug 2;372(9636):383-91

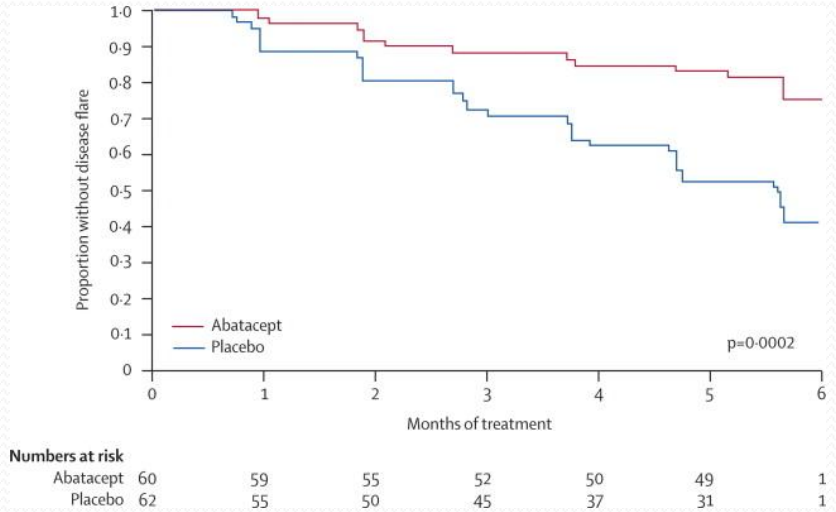
Abatacept in Polyarticular JIA



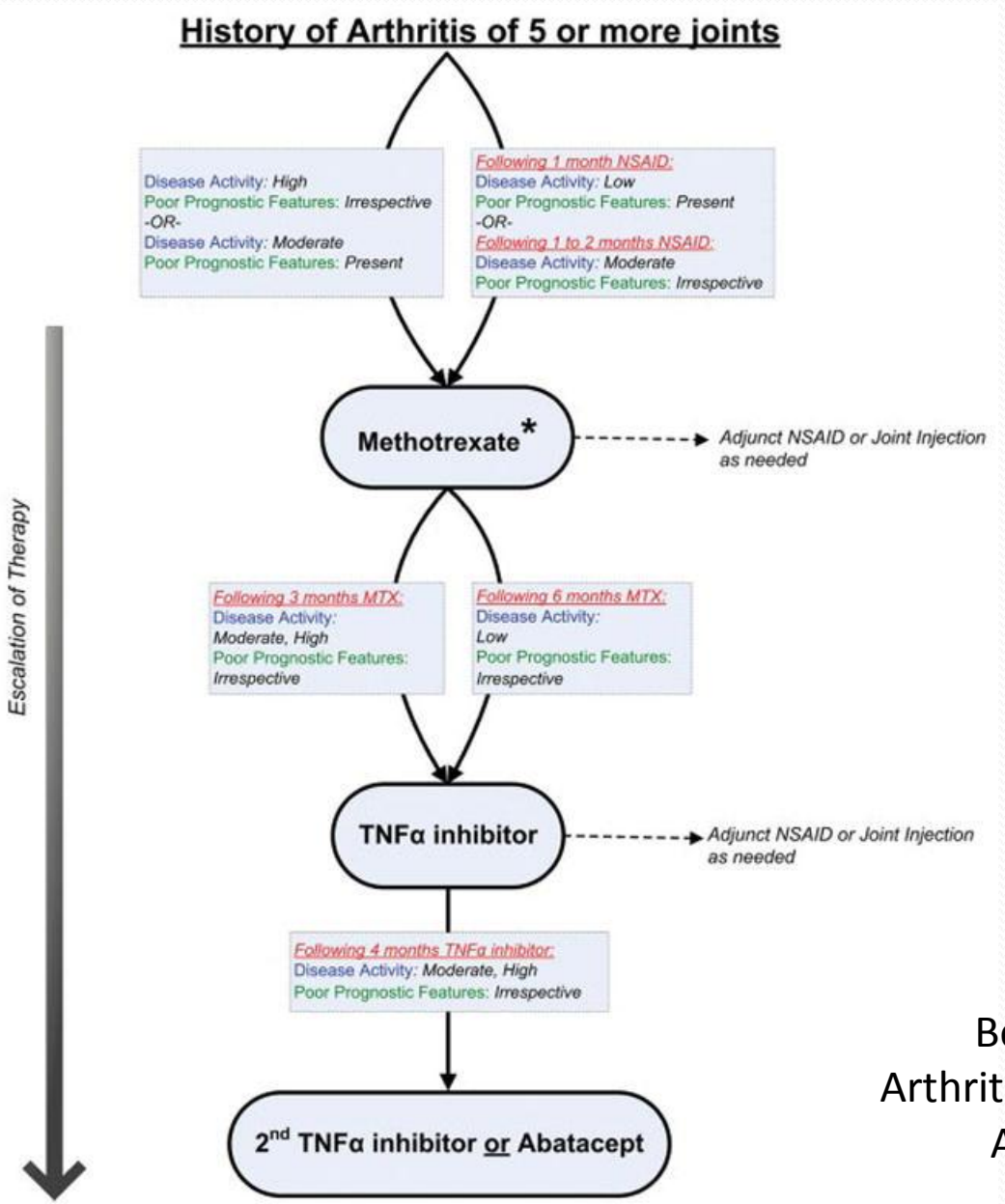
Ruperto N et al. Lancet. 2008 Aug 2;372(9636):383-91

Abatacept in Polyarticular JIA





Ruperto N et al. Lancet. 2008 Aug 2;372(9636):383-91



Beukelman T et al.
Arthritis Care Res. 2011
Apr;63(4):465-82.

Psoriatic Arthritis

- Arthritis and psoriasis, or arthritis and at least 2 of the following:
  - Dactylitis
  - Nail pitting or onycholysis
  - Psoriasis in a first-degree relative

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

Enthesitis Related Arthritis

- Arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:
  - The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
  - The presence of HLA-B27 antigen
  - Onset of arthritis in a male over 6 years of age
  - Acute (symptomatic) anterior uveitis
  - History of ankylosing spondylitis, enthesitis related arthritis, sacroiliiitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

Undifferentiated Arthritis

- Arthritis that fulfills criteria in no category or in 2 or more of the above categories

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

The other clinical categories

- **Active sacroiliac arthritis.**
  - *This group includes all patients with clinical AND imaging evidence of active sacroiliac arthritis. May include patients from any of the ILAR JIA categories.*
- **Systemic arthritis with active systemic features (and without active arthritis).**
  - *This group includes all patients who fulfill the ILAR criteria for systemic arthritis AND who have active fever of systemic JIA with or without other systemic features, but without active arthritis.*
- **Systemic arthritis with active arthritis (and without active systemic features).**
  - *This category includes all patients who fulfill the ILAR criteria for systemic arthritis AND who have active arthritis, but without active systemic features.*

Beukelman T et al. Arthritis Care Res. 2011 Apr;63(4):465-82.

Systemic Arthritis

- Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following:
  - Evanescent (nonfixed) erythematous rash
  - Generalized lymph node enlargement
  - Hepatomegaly and/or splenomegaly
  - Serositis

Petty et al. J Rheumatol. 2004 Feb;31(2):390-2

Systemic Arthritis – typical patient

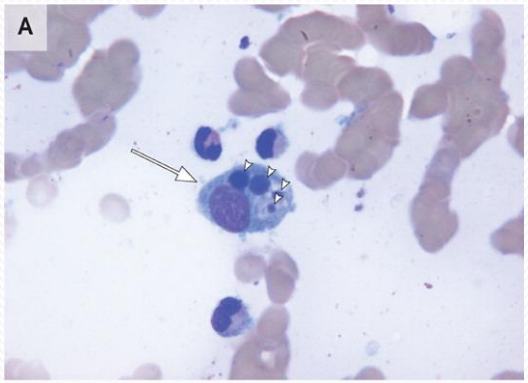
- Any age, even <1 year
- M=F
- Fever >38.5 for over 2 weeks
- Difficult to diagnose
  - Arthritis may not be dominant
  - Ill with high fevers, rashes, WCC and anaemia – infection and malignancies (especially leukaemia) need to be excluded

Systemic Arthritis – typical patient

- Typically 4-6 month period of spiking fevers and rash, with varying degrees of arthralgia and arthritis
- Arthritis resolves completely in 50%
- Recurrences years later are possible
  - Remission
  - Systemic (Fevers and rash – little arthritis)
  - Systemic + progressive arthritis
  - Resolution of systemic but relentless destructive arthritis of large and small joints

Systemic Arthritis – complications

- Macrophage activation syndrome (MAS)
  - Spontaneous bleeding, bruising, or shock, unremitting fever, lymphadenopathy, hepatosplenomegaly, and rash
  - Hemoglobin, platelet count, and serum fibrinogen typically drop precipitously secondary to consumptive coagulopathy
- Severe growth retardation
- Osteoporosis



Uttenthal BJ, Layton DM, Vyse TJ, Schreiber BE. NEJM 2012;366(23):2216-21.

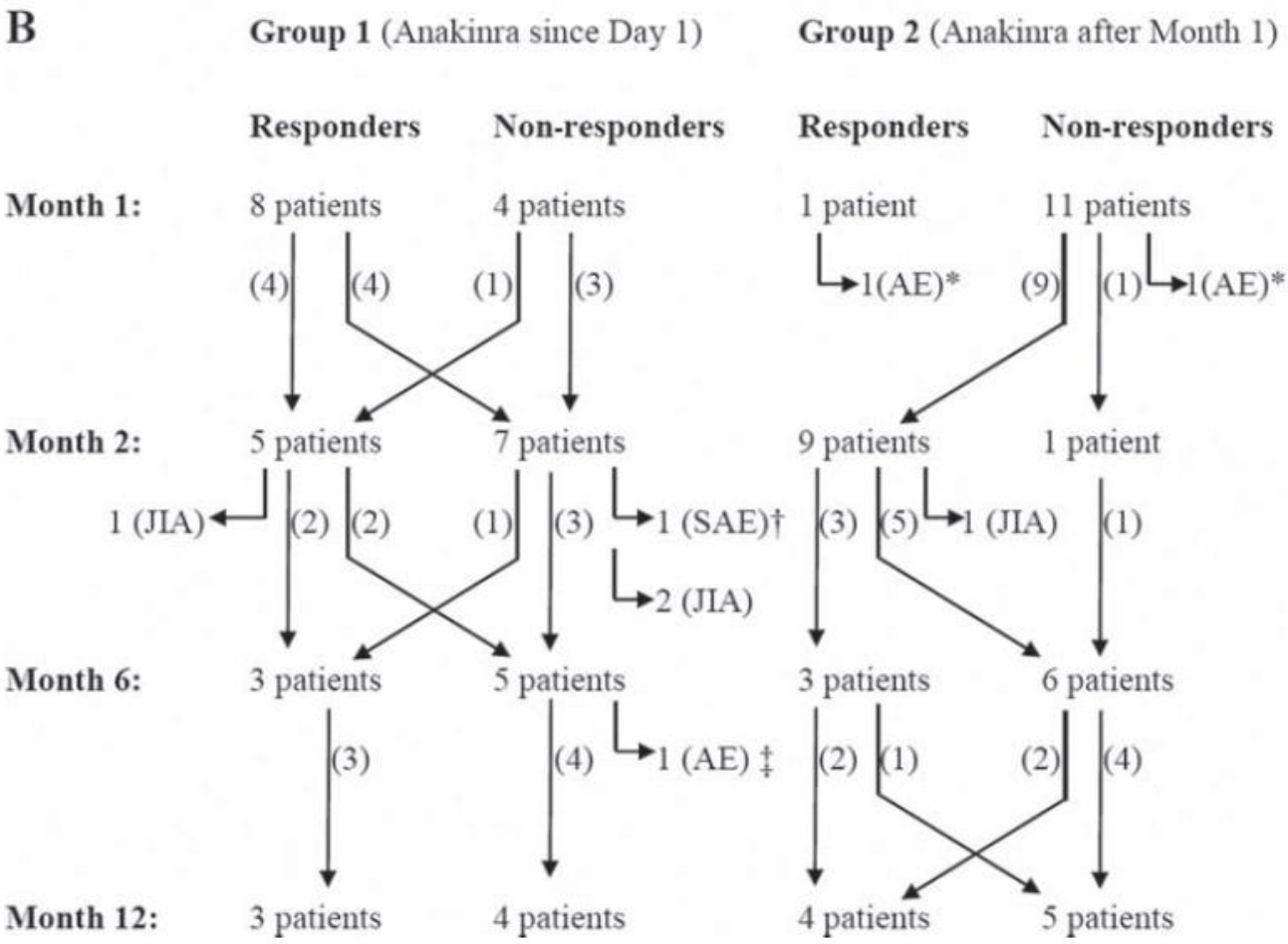
Anakina in systemic onset JIA

- Six centres (USA, France)
- Treatment group received anakinra (2 mg/kg subcutaneous daily, maximum 100 mg)
- Placebo group also did after one month
- Response
  - 30% improvement of the paediatric ACR criteria for JIA
  - resolution of systemic symptoms
  - Decrease of at least 50% of both CRP and ESR

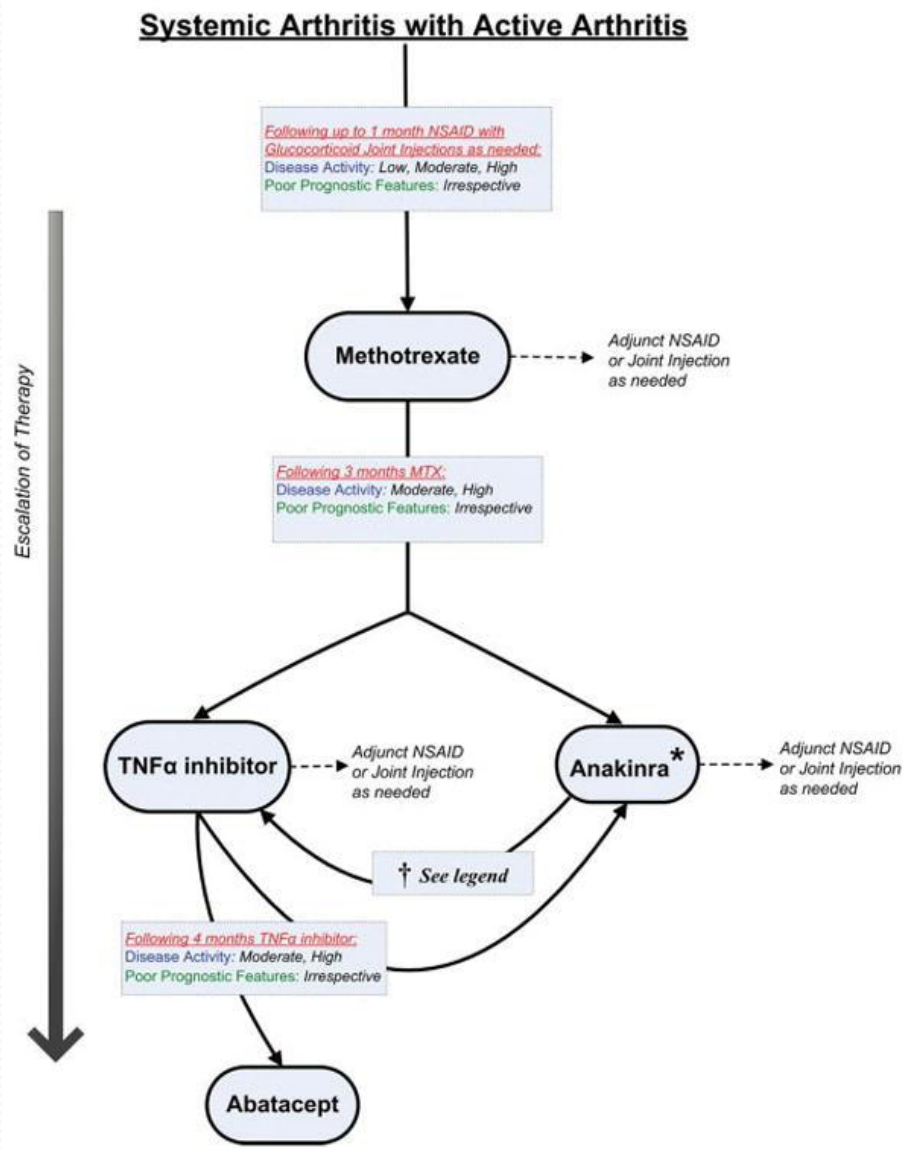
Characteristics	Anakinra (n = 12)	Placebo (n = 12)
Demographic features		
Female, n (%)	7 (58)	8 (67)
Age, mean value, years (SD)	9.5 (5.19)	7.5 (3.73)
Disease mean duration, years (SD)	4.2 (3.33)	3.2 (1.95)
Systemic features		
Fever (>38°C), no. of patients (%)	4 (33.3)	5 (41.7)
CRP, mg/l (n≤6), mean value (SD)	66 (64.40)	84 (65.74)
ESR first hour (n≤10), mean value (SD)	44 (23.37)	57 (27.85)
SAA, mg/l (n≤6.4), mean value (SD)	366 (262)	368 (229)
High serum ferritin*, no. of patients	2	3
Joint assessment		
Active joints, mean no. (SD)	16 (13.12)	16 (15.84)
Joints with LOM, mean no. (SD)	16 (14.88)	17 (14.91)
Global assessments		
Physician's VAS, mean value (SD)	63 (20.57)	57 (29.74)
Parent's global VAS, mean value (SD)	50 (24.39)	55 (26.51)
Parent's pain VAS, mean value (SD)	50 (25.73)	53 (25.89)
CHAQ, mean value (SD)	1.67 (0.845)	1.44 (0.625)
Treatment with steroids (predniso(lo)ne)		
Duration, mean, years (SD)	3.9 (2.93)	2.7 (2.10)
Daily dose, mean, mg/kg (SD)	0.52 (0.237)	0.66 (0.373)
Previous treatments with DMARDs, biological agents		
DMARD and/or biological agent, no. of patients	8	11
DMARD, no biological agent, no. of patients	3	3
DMARD and biological agent, no. of patients	5	8
Methotrexate, no. of patients	8	11
Etanercept, no. of patients	5	8
Others, no. of patients (no. of DMARDs)	4 (7†)	4 (6‡)

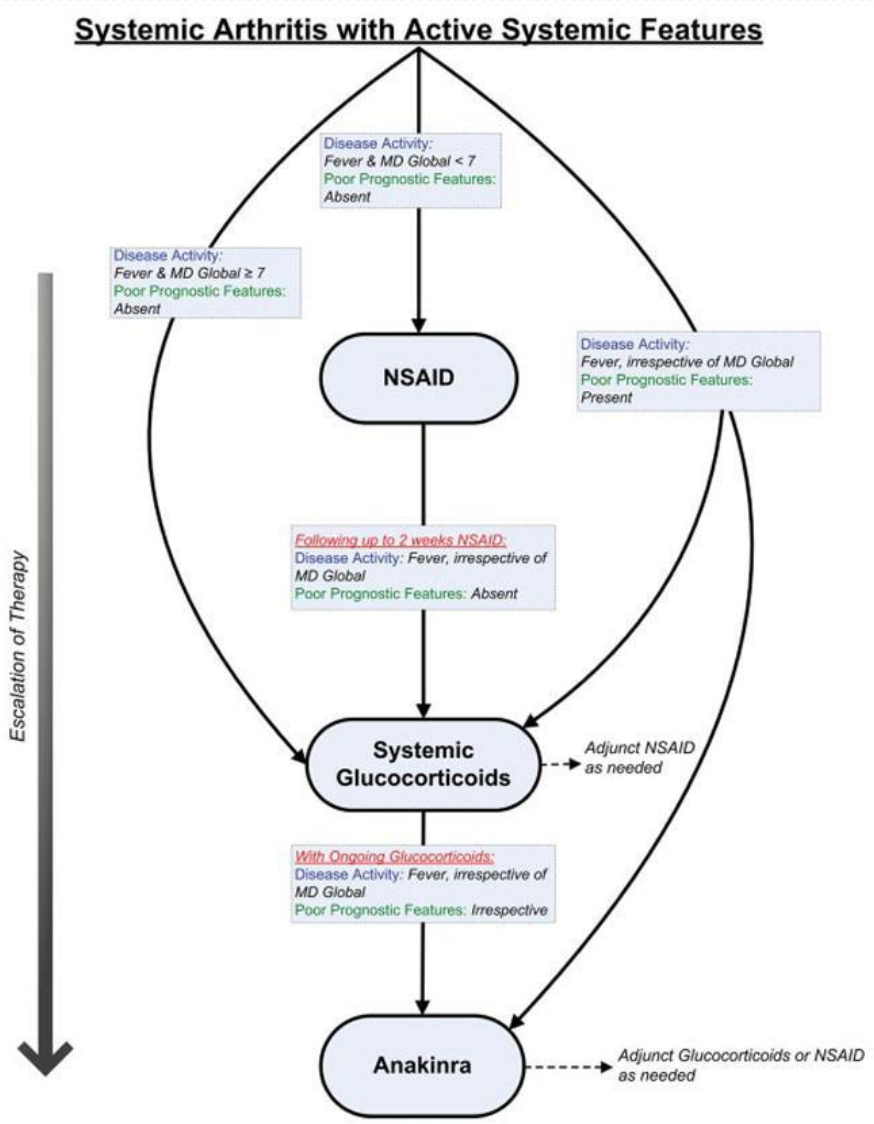
ANAJIS trial. Ann Rheum Dis. 2011 May;70(5):747-54

Anakina in systemic onset JIA



Ann Rheum Dis. 2011 May;70(5):747-54



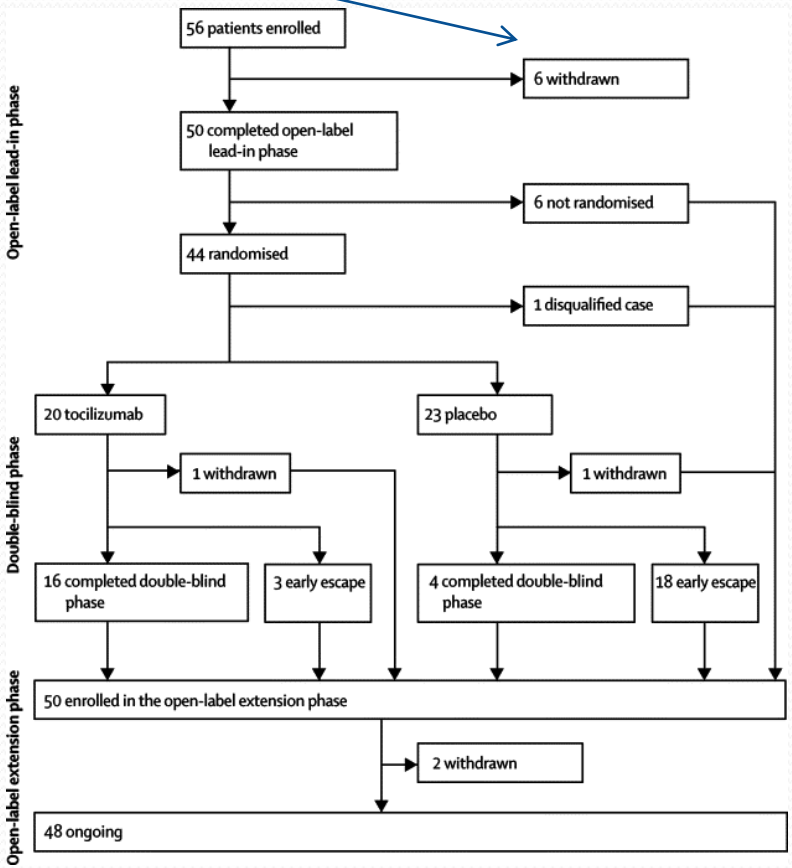


Beukelman T et al. Arthritis Care Res. 2011 Apr;63(4):465-82.

Tocilizumab

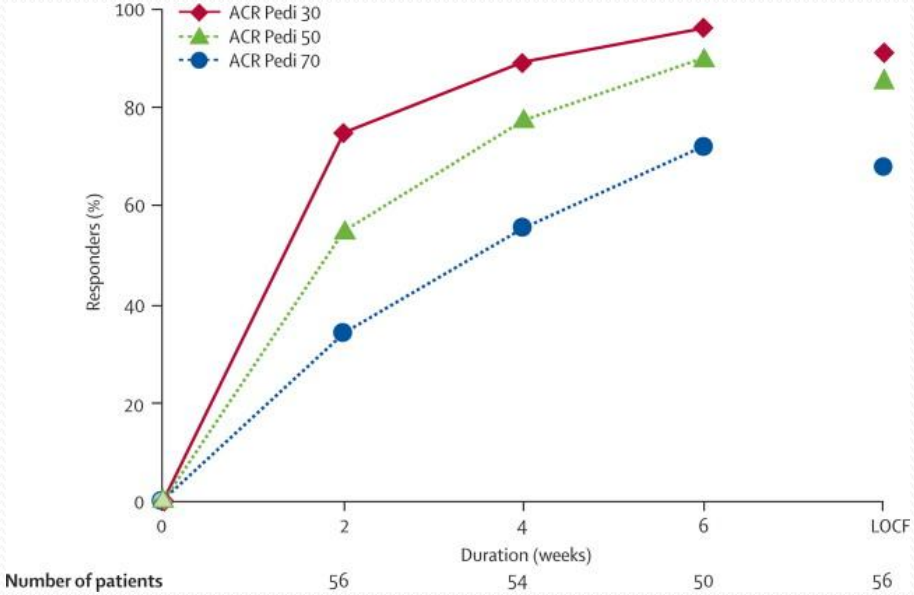
Six patients were withdrawn during the open-label lead-in phase: three developed anti-tocilizumab IgE antibodies, two had serious adverse events (one anaphylactoid reaction, one gastrointestinal haemorrhage), and one because of absence of efficacy

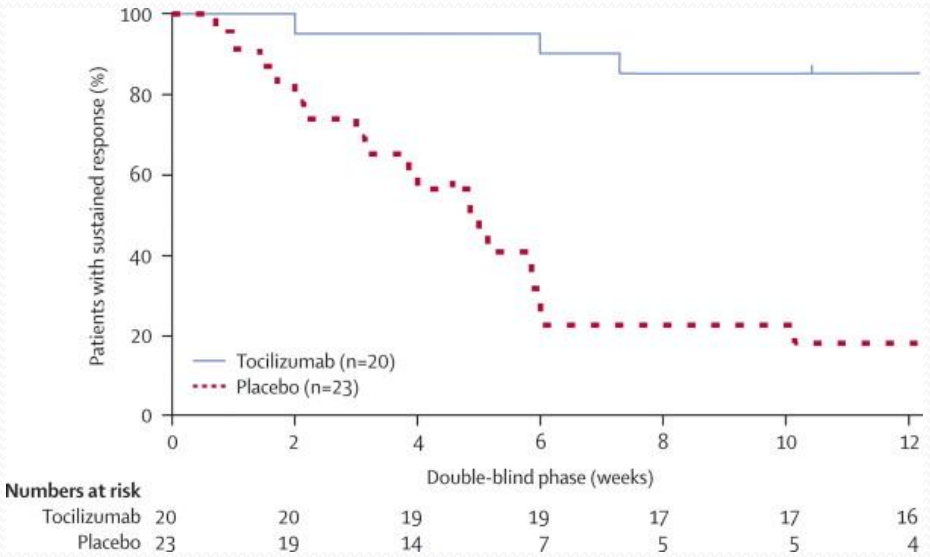
- Randomised, double-blind, placebo-controlled withdrawal trial.
- 56 children, aged 2-19
- Given tocilizumab 8mg/kg every 2 weeks for 6 weeks
- Responders (ACR Pedi 30 and CRP <5) entered into RCT



Yokota S et al. Lancet. 2008 Mar 22;371(9617):998-1006.

Tocilizumab in Systemic onset JIA





Yokota S et al. Lancet. 2008 Mar 22;371(9617):998-1006.

NICE guidance

- Tocilizumab is recommended for the treatment of systemic JIA (Dec 2011)
  - in children and young people aged 2 years and older
  - whose disease has responded inadequately to NSAIDs, systemic corticosteroids and methotrexate
- Etanercept is recommended
  - for children aged 4 to 17 years who have active JIA in at least five joints and whose condition has not responded adequately to methotrexate or who have been unable to tolerate treatment with methotrexate.

The Need for Transition

- For young people with long term conditions the move to adult services means a shift from being ‘special’, in the sheltered atmosphere of a small children’s service; into an environment with
  - many older patients
  - less social support
  - clinicians may have less time
  - clinical practice may be focused on the older end of the age range, and
  - the family may be excluded.
  - Staff may have little interest and few skills in dealing with ‘difficult’ adolescents.

Getting the right start: *National Service Framework* for Children, Young People and Maternity Services: Standard for hospital services, DoH 2003.

The Need for Transition

- The risk
  - If transfer to adult services is handled badly, there is a risk that the young person will ‘drop out’ from medical services altogether.
  - There is some evidence that properly planned transition programmes result in better disease control and improved patient satisfaction.

Getting the right start: *National Service Framework* for Children, Young People and Maternity Services: Standard for hospital services, DoH 2003.

Adolescent Rheumatology Service

- **Children under 19 in full time education**
- **Fully BSPAR compliant**
  - Level 3 child Protection Training
  - Clinical Network (adult rheum + gen paed with tertiary centre @ UCH)
  - Multidisciplinary team
- **Meet ARMA standards of care**
  - Children and young people in whom juvenile idiopathic arthritis is suspected should be seen within a maximum of 4 weeks from the date of referral
  - For children and young people, particular consideration should be given to education and developmental needs.
  - There should be an identified clinical specialist who is responsible for transitional care when children transfer from paediatric to adult care.
- **First clinic September 4th!**