IL-6

DEL LABORATORIO A LA PRACTICA

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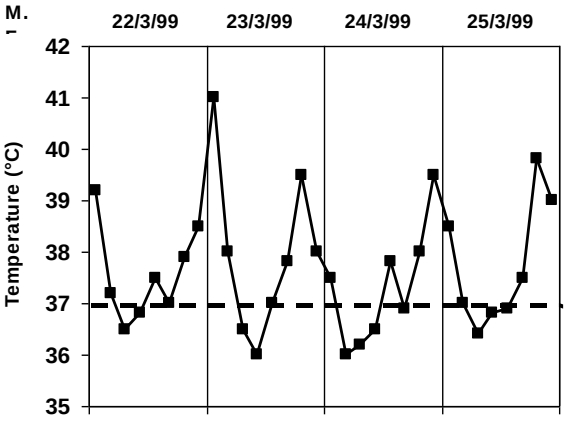
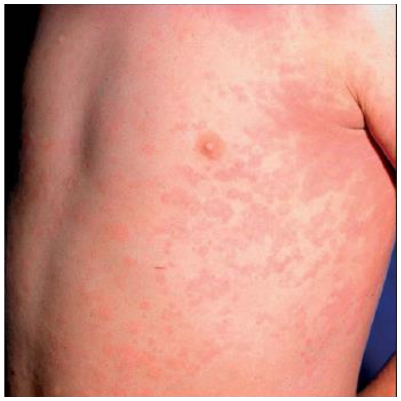
OSPEDALE PEDIATRICO

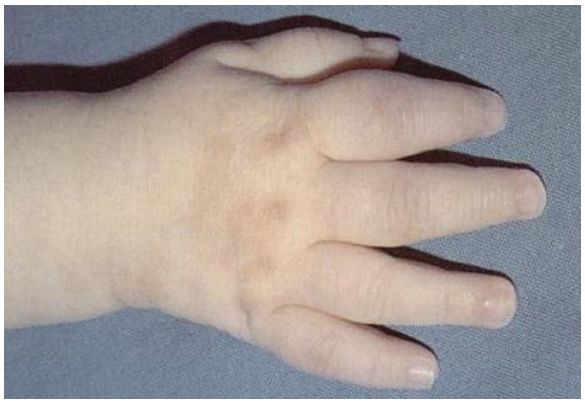
Systemic Juvenile Idiopathic Arthritis

10% of all children with JIA

Chronic arthritis associated with high spiking fever and other systemic features (rash, hepato- splenomegaly, serositis) and prominent acute phase response



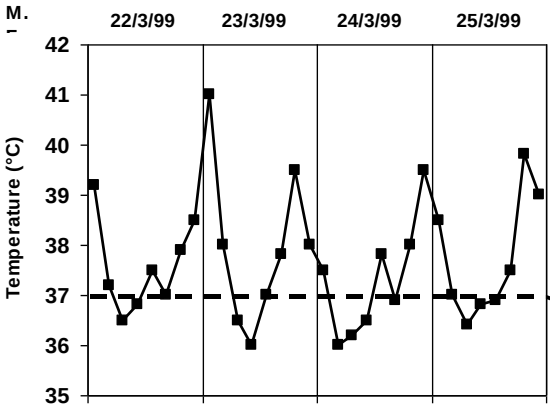


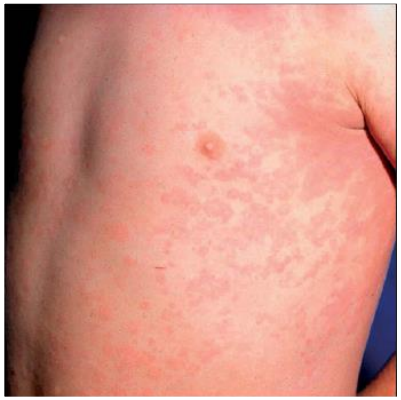


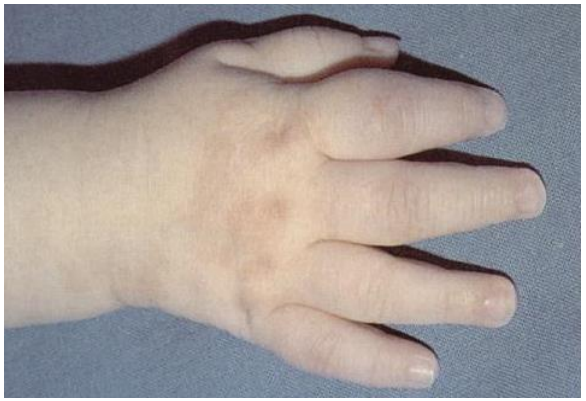
Systemic Juvenile Idiopathic Arthritis

Disease course (Lomater J rheumatol 2000)

- **Monocyclic course**
- **Polyciclic course: Recurrent flares of fever and arthritis**
- **Persistent course:**
  - **Systemic flares with persistence of arthritis**
  - **Persistence of both systemic features and arthritis**





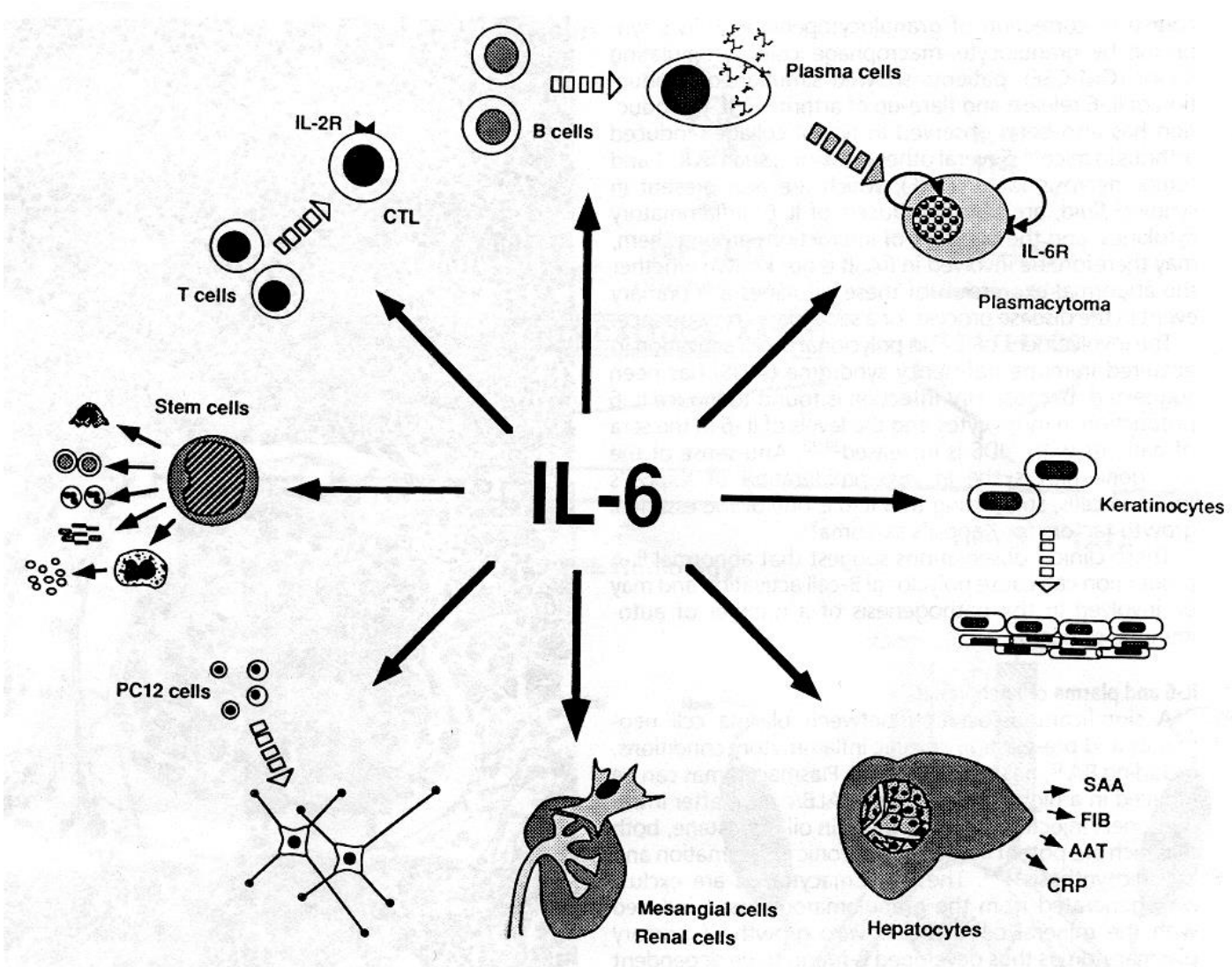


Systemic juvenile idiopathic arthritis

- **No associations with HLA alleles[1,2]**
- **Absence of autoantibodies or autoreactive T cells[1,2]**
- **Systemic manifestations[3]**
  - **High spiking fever, skin rash, lymphoadenopathy, liver and spleen enlargement, serositis**
- **Complications**
  - **Systemic osteoporosis, stunted growth, macrophage activation syndrome[3,4]**
- **Prominent laboratory features of inflammation[3]**
  - **Marked increase in ESR, and CRP, leucocytosis, thrombocytosis, microcytic anaemia**

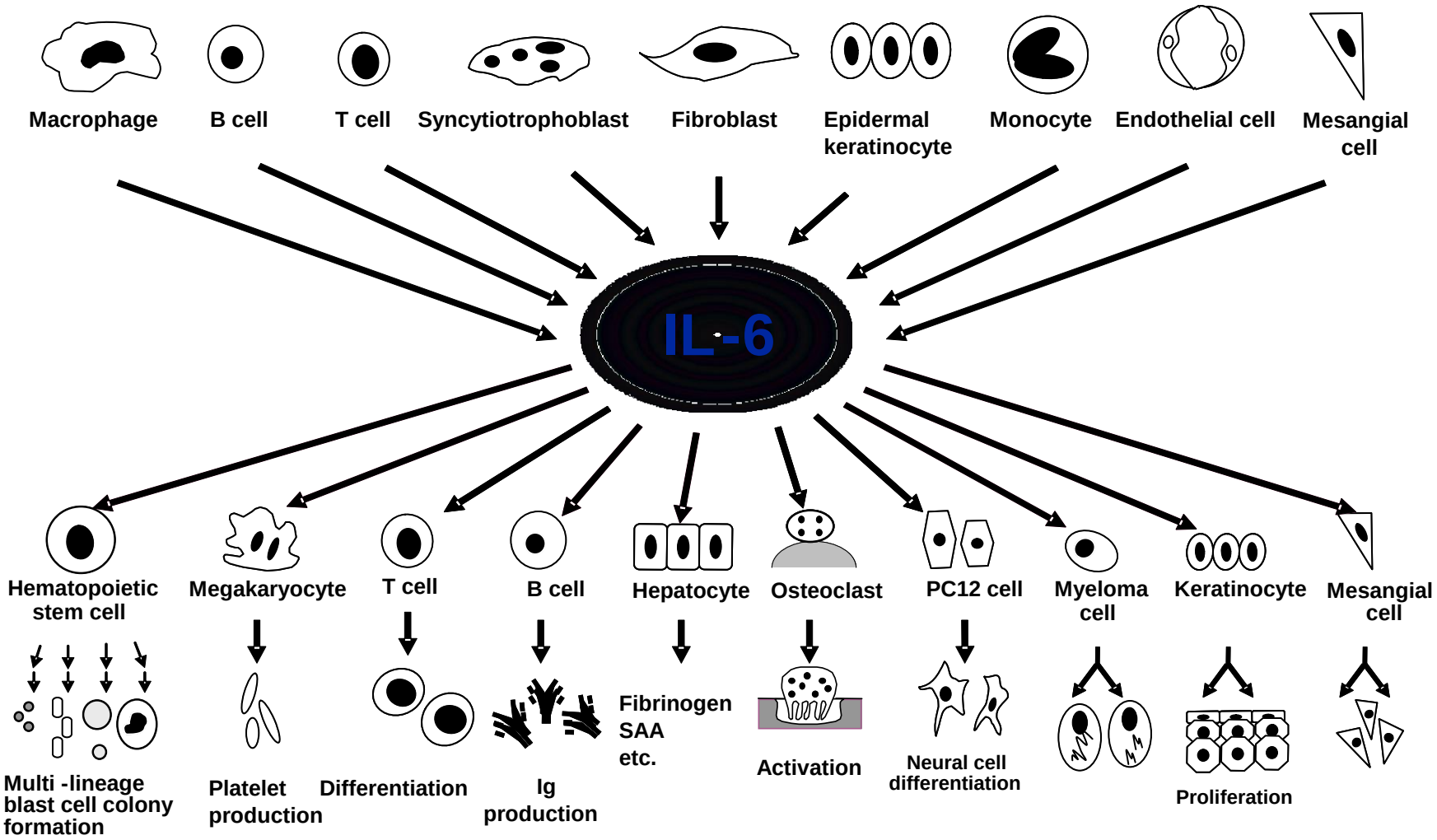
1. Vastert S, *et al. Best Pract Res Clin Rheumatol* 2009; **23**:655–644;
2. Woo P & Colbert R. *Best Pract Res Clin Rheumatol* 2009; **23**:589–597;
3. Schneider R & Laxer RM. *Clin Rheumatol* 1998; **12**:245–271; 4. Woo P, *et al. Nat Clin Pract Rheumatol* 2006; **2**:28–34.

IL-6: multiple biological activities



Hirano T et al, Immunol Today 1990

IL-6: 10 years later
Multiple sources and targets

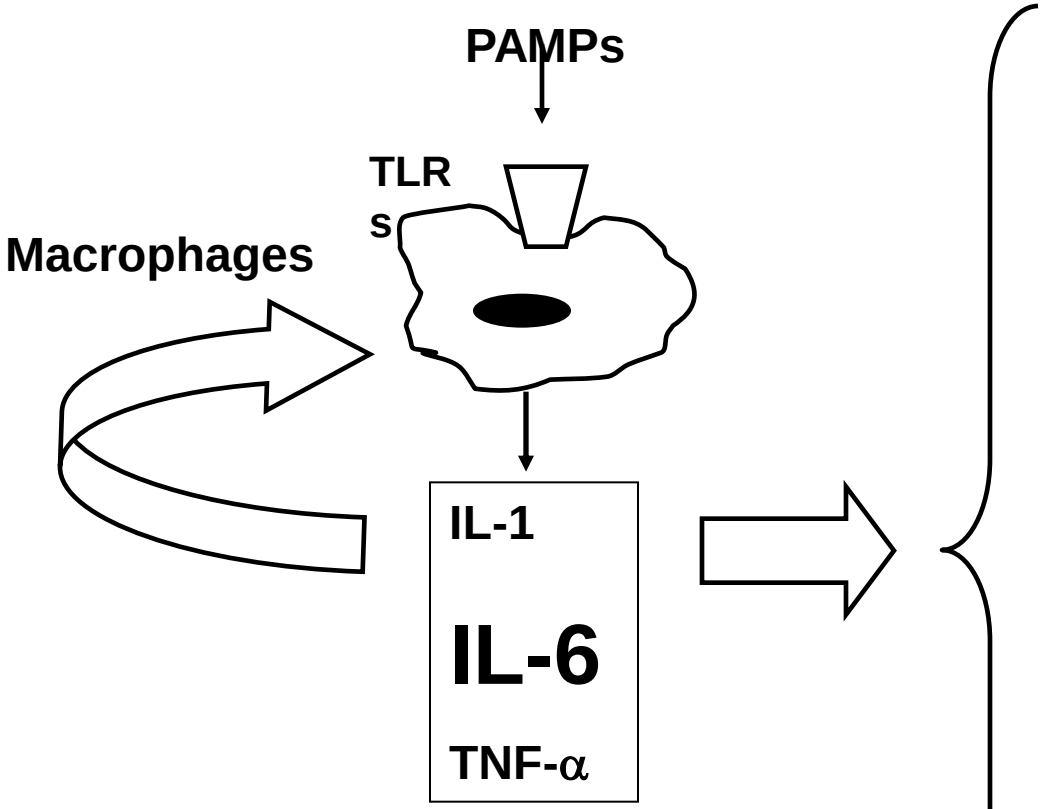


Naka T, *et al. Arthritis Res* 2002; 4(Suppl 3):S233–S242.

Agenda

- **Role in systemic and local inflammatory responses**
- **IL-6 as target in s-JIA**
- **Anti-IL-6 treatment in s-JIA**
- **IL-1 and IL-6: in vitro and in vivo interplay**

IL-6 and the systemic inflammatory response



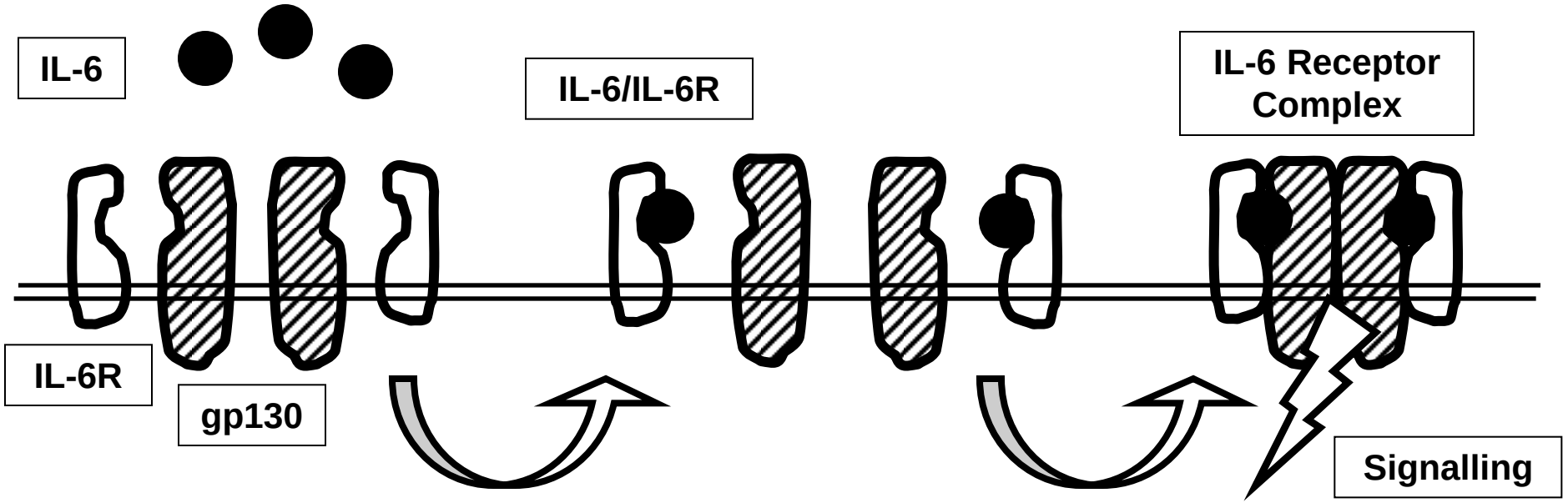
CNS
- fever
- sleep behaviour
- anorexia
- HPA axis activation

BONE MARROW
- granulocytopoiesis
- thrombocytopoiesis

LIVER
- acute phase response

SOMATIC TISSUES
- muscle proteolysis
- adypocyte lipolysis

The IL-6 receptor



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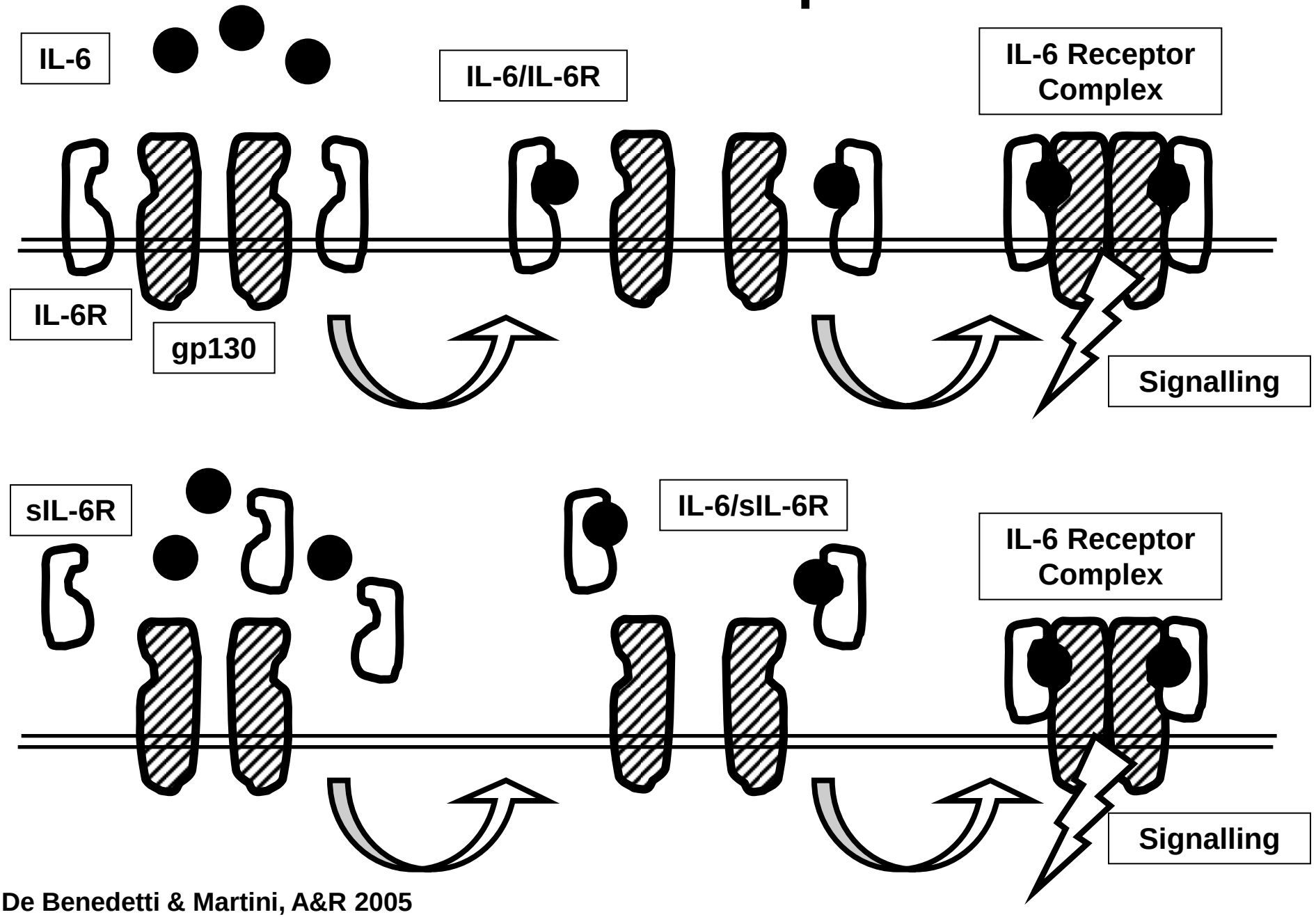


De Benedetti & Martini, A&R 2005

The soluble IL-6 receptor (sIL-6R)

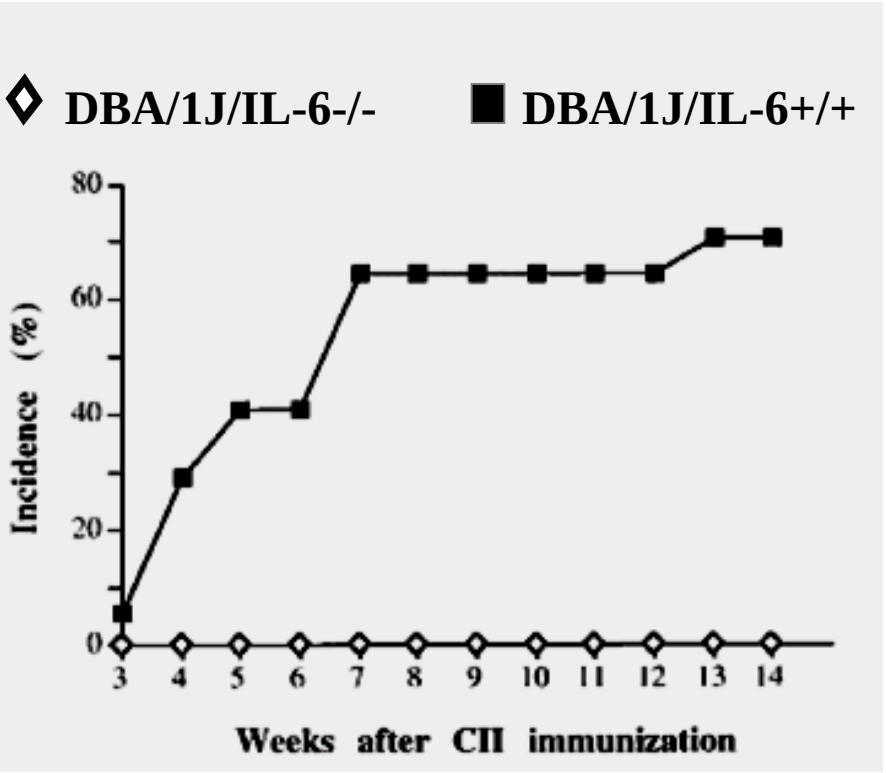
- **Produced by differential mRNA splicing**
- **Present at ng/ml concentration in body fluids**
- **Binds IL-6 with same affinity as the membrane IL-6R**
- **Acts as a carrier protein**
- **Increases plasma IL-6 half-life**
- **IL-6/sIL-6R complex binds gp130 with same affinity as the IL-6/IL-6R complex**

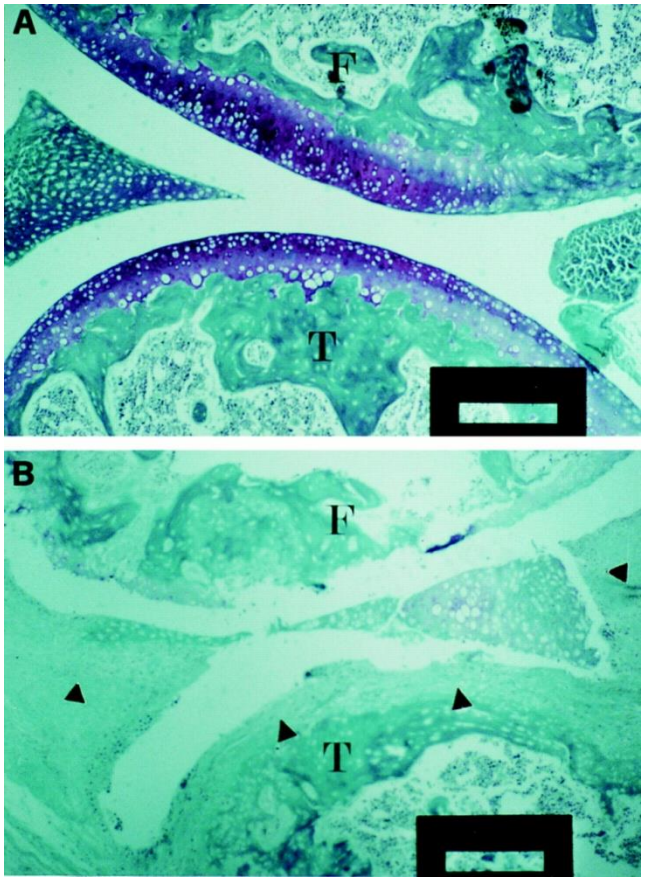
IL-6 and the local inflammatory response in the joints

- **expression of adhesion molecules and production of chemokines by endothelium**
- **proliferation of B and T lymphocytes**
- **proliferation of synovial fibroblasts**
- **differentiation and activation of osteoclasts**
- **decreased production of matrix protein by chondrocytes**

Interleukin 6 Is Required for the Development of Collagen-induced Arthritis

By Tonino Alonzi,* Elena Fattori,* Domenico Lazzaro,*
Patrizia Costa,* Lesley Probert,‡ George Kollias,‡
Fabrizio De Benedetti,§ Valeria Poli,* and Gennaro Ciliberto*



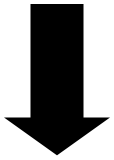


IL-6-/-

IL-6+/+

Arthritis
Effects of IL-6 ablation in mice

- **SKG mice**
  - **(Hata H, J Clin Invest 2004)**
- **Collagen-induced arthritis**
  - **(Alonzi T, J Exp Med 1998)**
- **Antigen-induced arthritis**
  - **(Ohshima S, PNASS 1998, Boe A, Cytokine 1999)**
- **Zymosan-induced arthritis**
  - **(de Hooge ASK, Am J Pathol 2000)**



Absence/reduction of inflammatory infiltrate

- **Role in systemic and local inflammatory responses**
  - **Unique biology of the soluble IL-6 receptor**
  - **Role in mononuclear cell recruitment**
- **IL-6 as target in s-JIA**
- **Anti-IL-6 treatment in s-JIA**
- **IL-1 and IL-6: in vitro and in vivo interplay**
- **Future of IL-6 inhibition**

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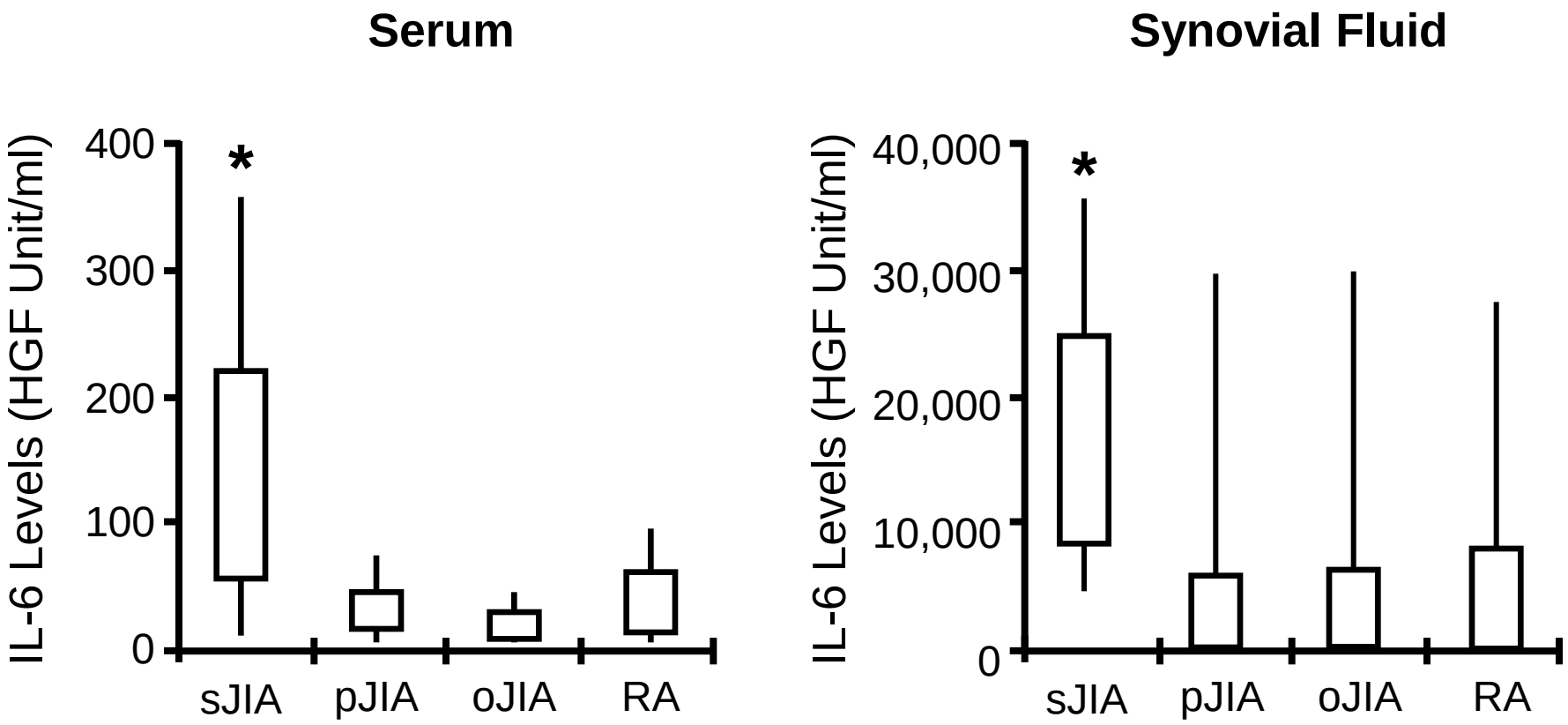
IL-6 in systemic juvenile idiopathic arthritis



pJIA = polyarticular JIA, oJIA = oligoarticluar JIA
* *p*<0.001 vs other arthritides

De Benedetti F, *et al. Arthritis Rheum* 1991; **34**:1158–1163.
De Benedetti F, *et al. Clin Exp Rheumatol* 1992; **10**:493–498.
De Benedetti F, *et al. J Rheumatol* 1997; **24**:1403–1409.

IL-6 in systemic JIA

- **Markedly elevated serum and SF levels**
- **Spontaneous production by peripheral blood monocytes and abnormal regulation of production (Pignatti P et al 2001)**
- **Association with a promoter polymorphism (Fishman D et al 1998, Ogilvie EM et al 2003)**

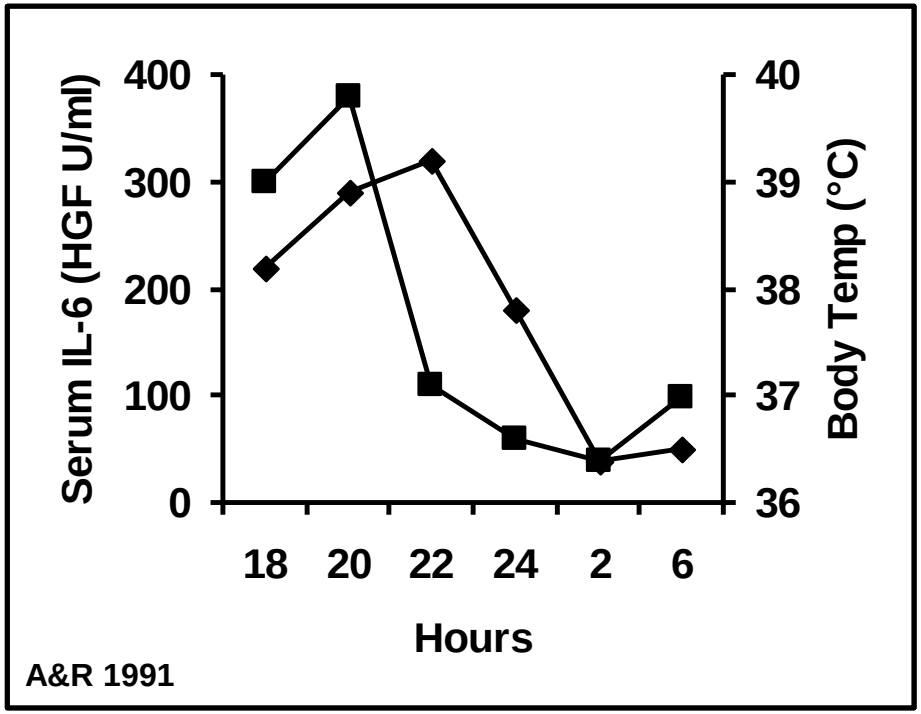
⇩

<u>Associations with clinical and laboratory systemic features</u>

IL-6 and the fever peak in systemic JIA

IL-6 gene expression is necessary for fever response to LPS or IL-1β: a study on IL-6-deficient mice.

Chai Z et al J Exp Med 1996



- **Rooney, Br J Rheumatol 1995**

↑ **IL-6**

No increase IL-1β

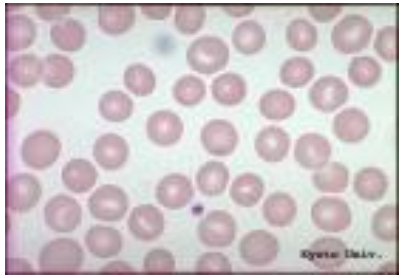
- **Prieur, Rev Rhum Engl Ed 1996**

↑ **IL-6**

No increase: IL-1α, IL-1β, TNFα

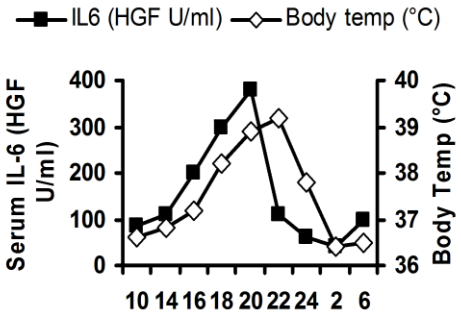
Prominent Interleukin-6 production in systemic JIA

Anemia



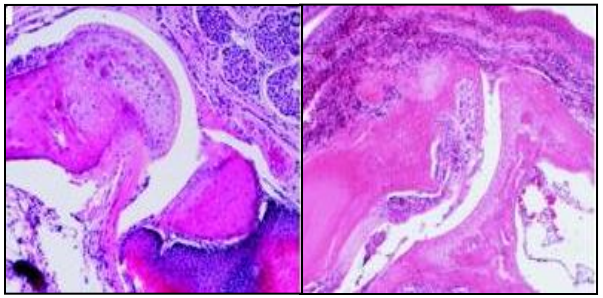
Lancet 1995
Blood 1996

Fever



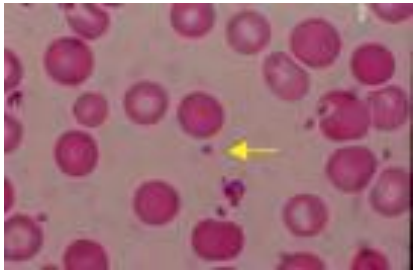
A&R 1991

Joint Inflammation



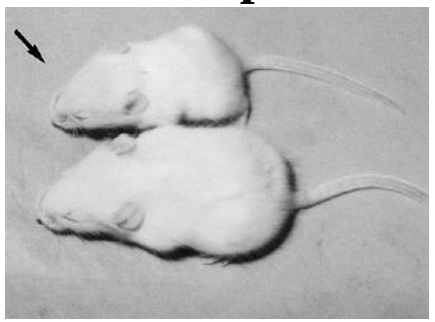
J Exp Med 1998

Thrombocytosis



A&R 1991

Growth Impairment

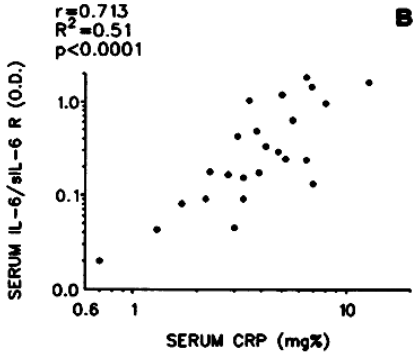


J Clin Invest 1997
Endocrinol 2001

Osteoporosis

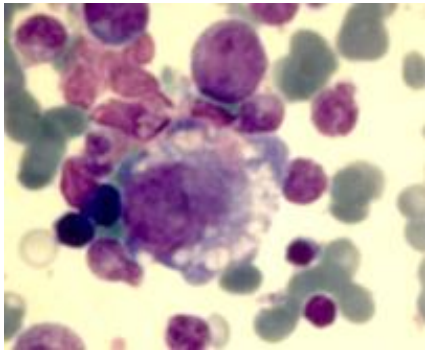
A&R 2006

IL6/soluble IL6R and CRP



J Clin Invest 1994

MAS



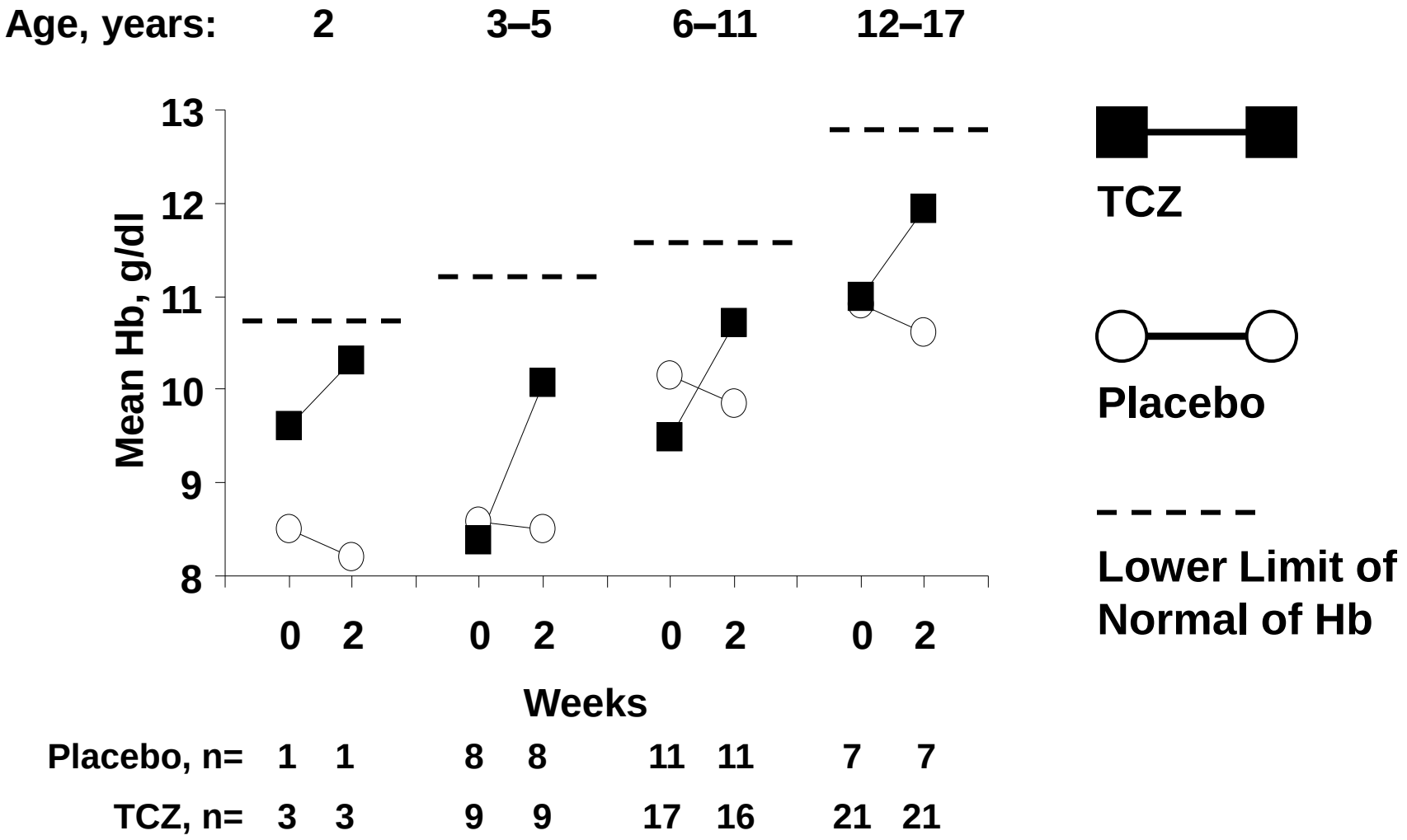
IL-6 and anaemia: in vivo

	sJIA	s.c. (humans)	i.p. (rats)	Transgenic mice	Turpentine (mice or rats)
Hb[1,2,3]	↓	↓	↓	↓	↓
MCV[1]	↓	↓		↓	
Pl. Iron[4]	↓	↓	↓	↓	↓
Ferritin[4]	↑	↑	↑		↑
RE iron uptake[5]			↑		↑
Iron absorption[6]	↓ ?				↓
EPO Production[1,7]	N	N			
BFU-E proliferation[8]	N	N		N	

Hb = haemoglobin;
MCV = mean corpuscular volume;
RE = reticulo-endothelial ;
EPO = erythropoietin;
BFU-E = erythroid burst forming units

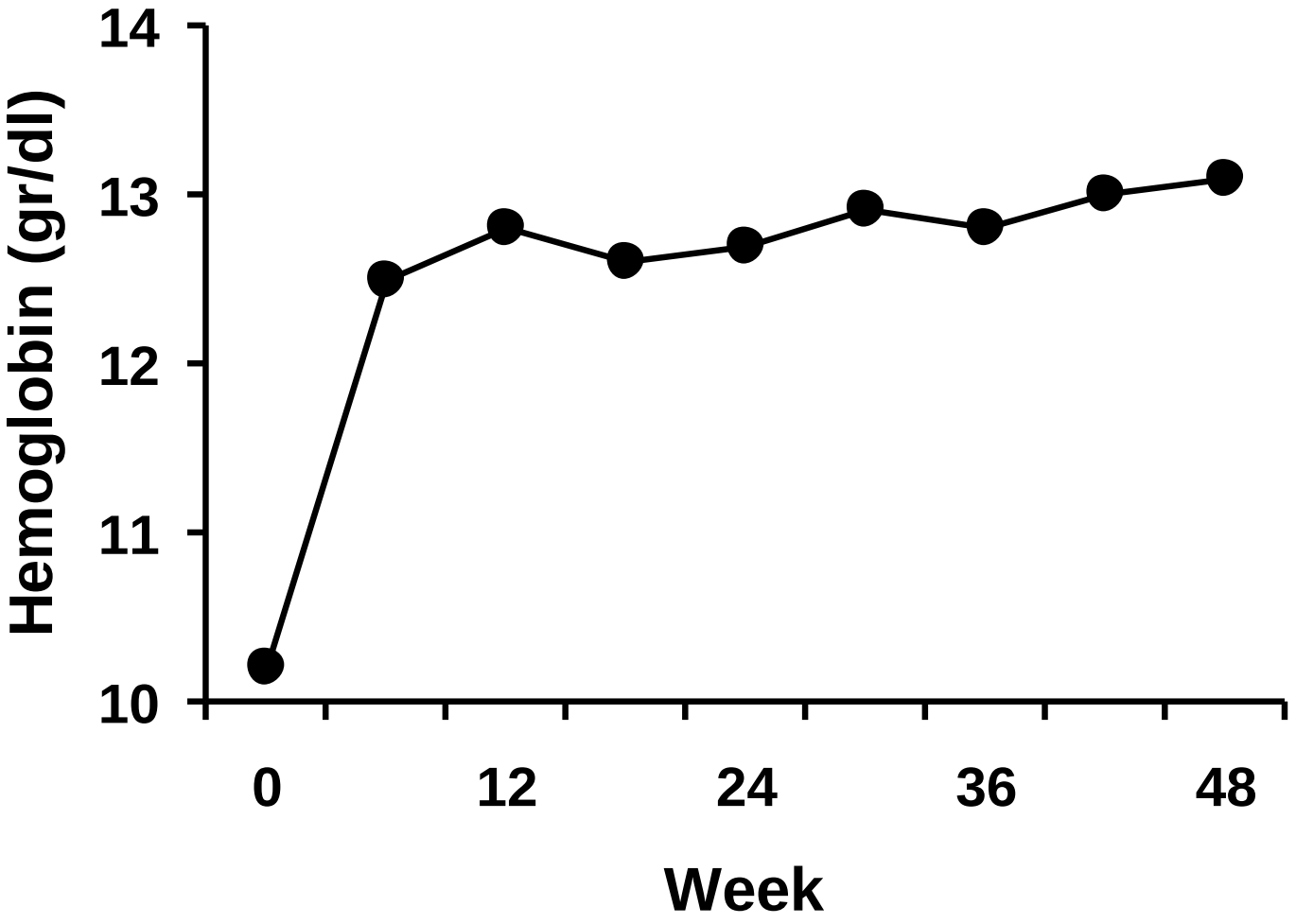
1. Cazzola M, *et al. Blood* 1996; **87**:4824–4830.
2. Jongen-Lavrenvic M, *et al. Clin Exp Immunol* 1996:**103**;328–334.
3. Atkins MB, *et al. Blood* 1995: **86**;1288–1491.
4. Savin MA and Cook JD. *Blood* 1980; **56**:1029–1035.
5. Hirayama M, *et al. Hepatology* 1993; **18**:874–880.
6. Kobune M, *et al. Hepatology* 1994; **19**:1468–1475.
7. Faquin WC, *et al. Blood* 1992; **79**:1987–1994.
8. Sul X, *et al. J Exp Med* 1996; **183**:837–845.

TENDER: Early changes in haemoglobin levels in TCZ treated sJIA patients



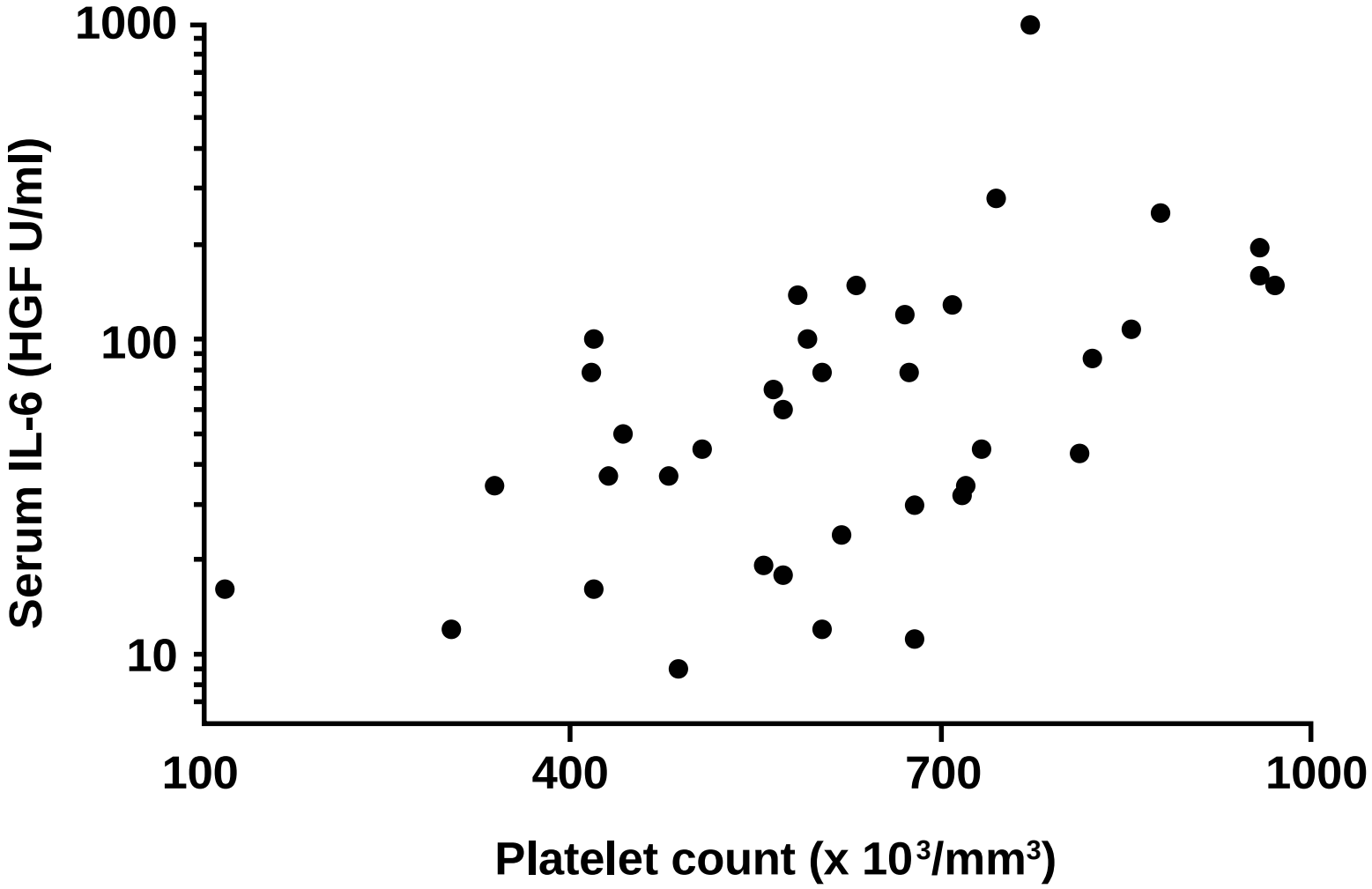
Roche: data on file.

TENDER: Changes in hemoglobin levels in TCZ treated s-JIA patients



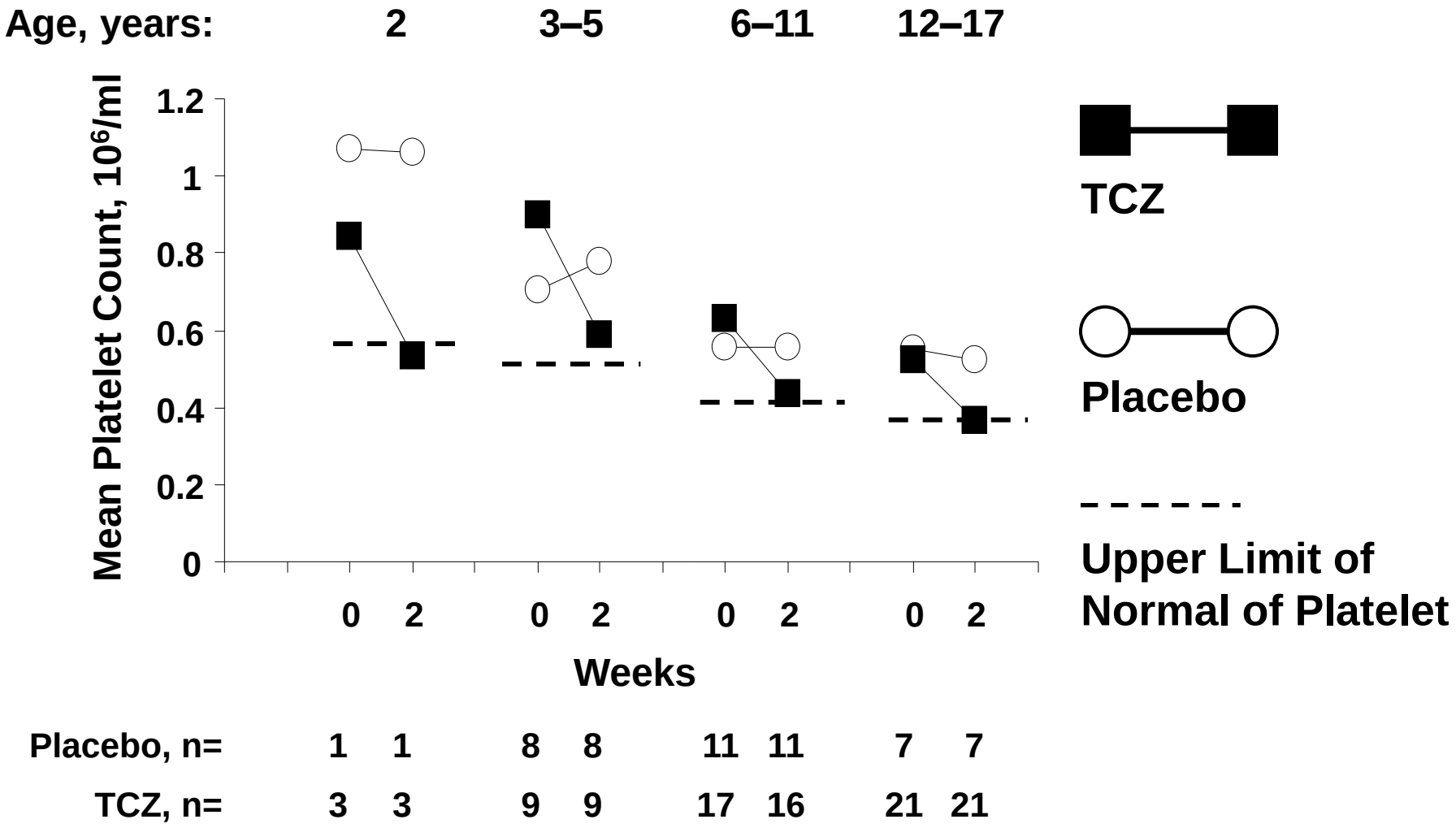
Roche: data on file

IL-6 and thrombocytosis in sJIA



De Benedetti F, *et al. Arthritis Rheum* 1991; **34**:1158–1163.

TENDER: Early changes in platelet counts in TCZ treated sJIA patients



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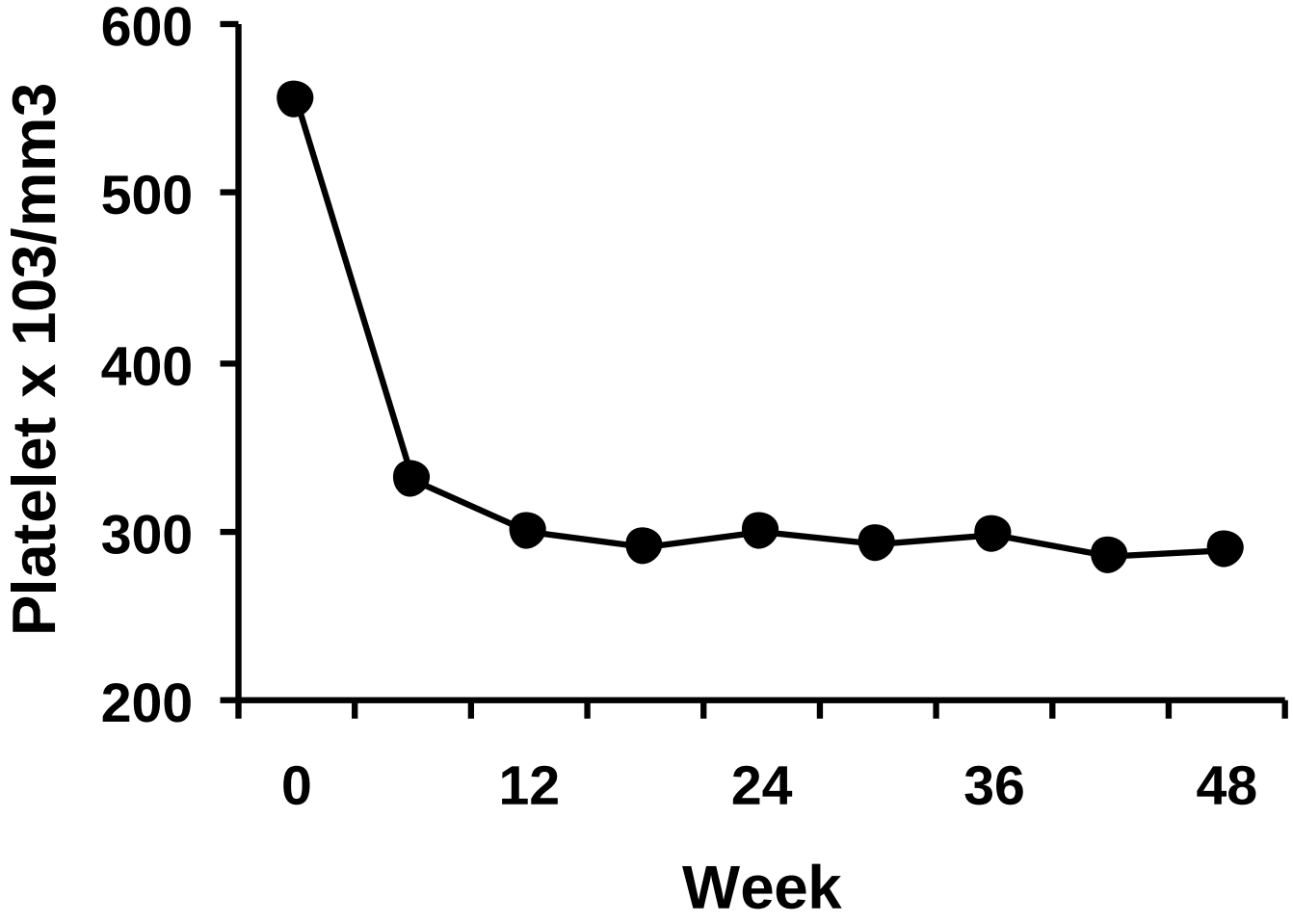
TENDER: Changes in platelet counts in TCZ treated s-JIA patients



Roche: data on file

- **Role in systemic and local inflammatory responses**
  - **Unique biology of the soluble IL-6 receptor**
  - **Role in mononuclear cell recruitment**
- **IL-6 as target in s-JIA**
  - **The rational and the use of anti-IL-6 Tx as a probe for proof of concept**
- **Anti-IL-6 treatment in s-JIA**
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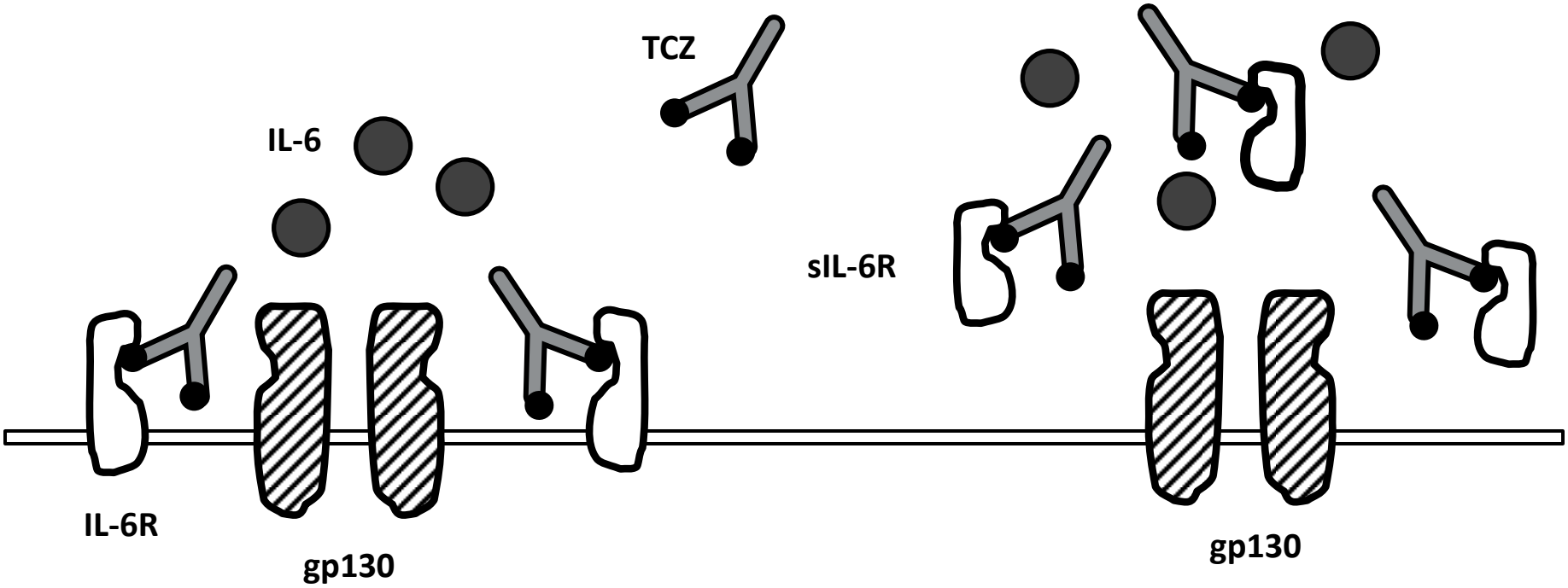
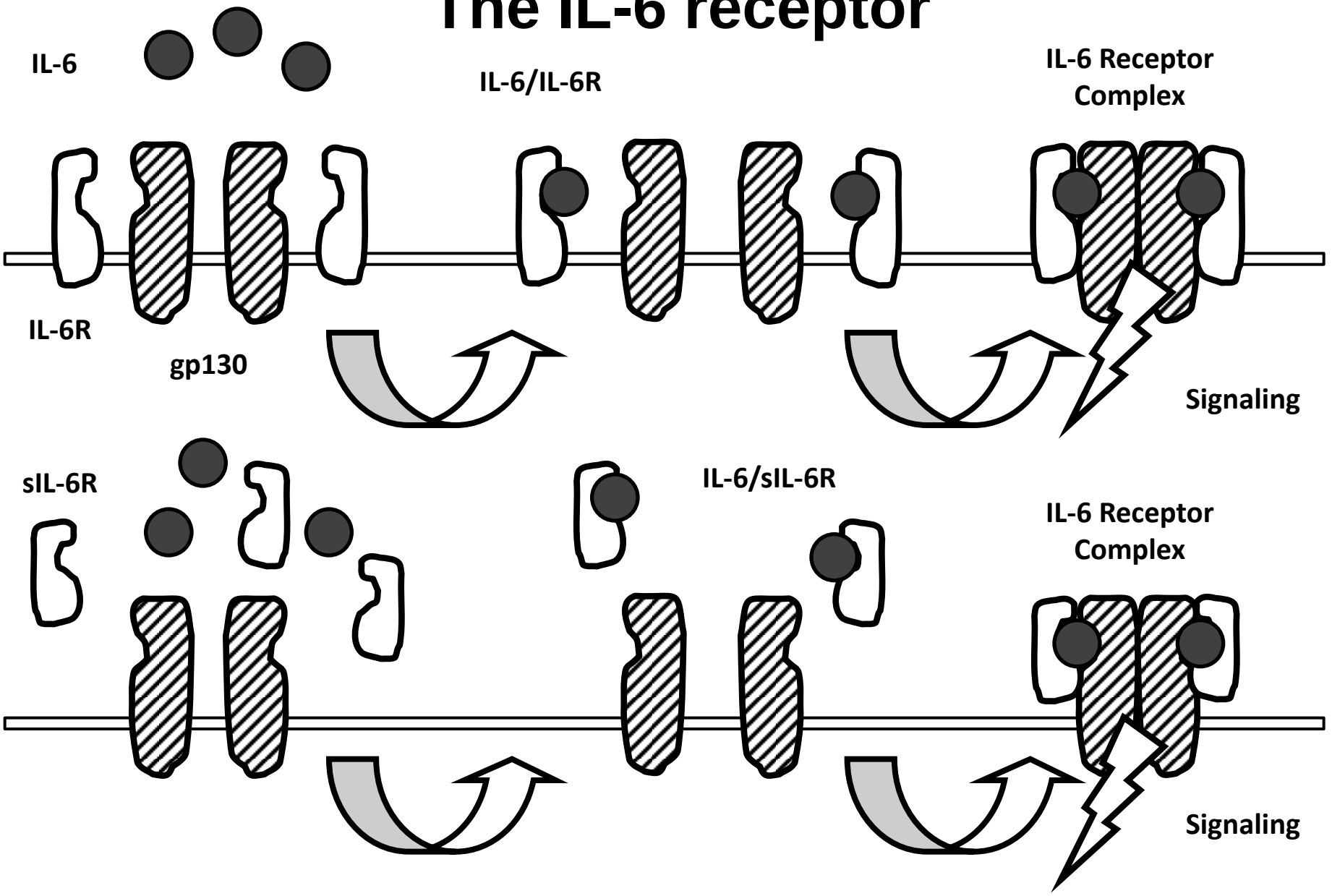
Tocilizumab (TCZ)
A humanized MoAb against the IL-6R



MoAb = monoclonal antibody

Based on: De Benedetti F & Martini A. *Arthritis Rheum* 2005; **52**:685–693.

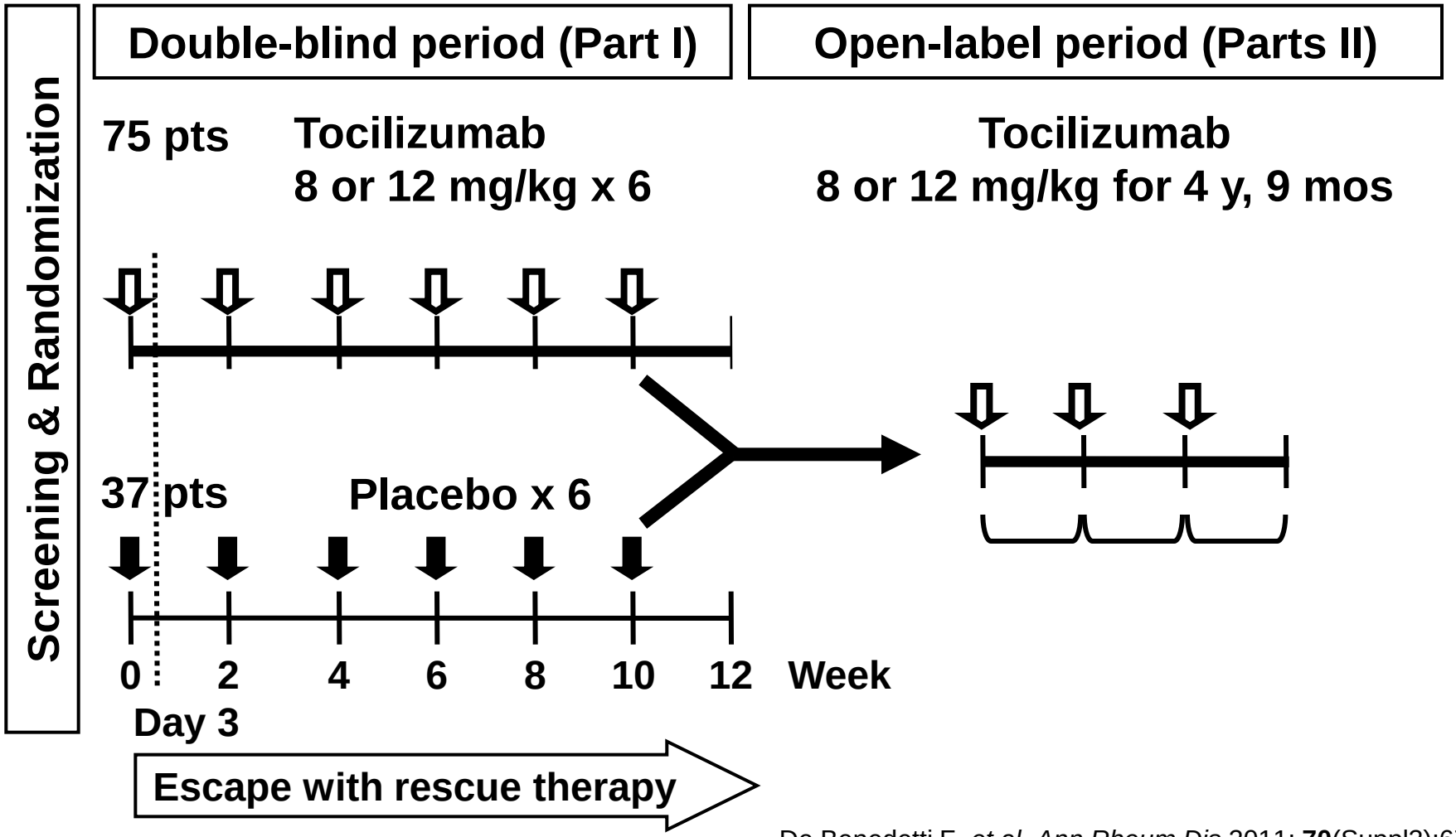
The IL-6 receptor



De Benedetti F & Martini A. *Arthritis Rheum* 2005; **52**:685–693.

TENDER: A 12-week randomized, double-blind, placebo-controlled, parallel group, 2-arm study (Part I) with a 5-year single arm open-label extension (Parts II)

Study Design



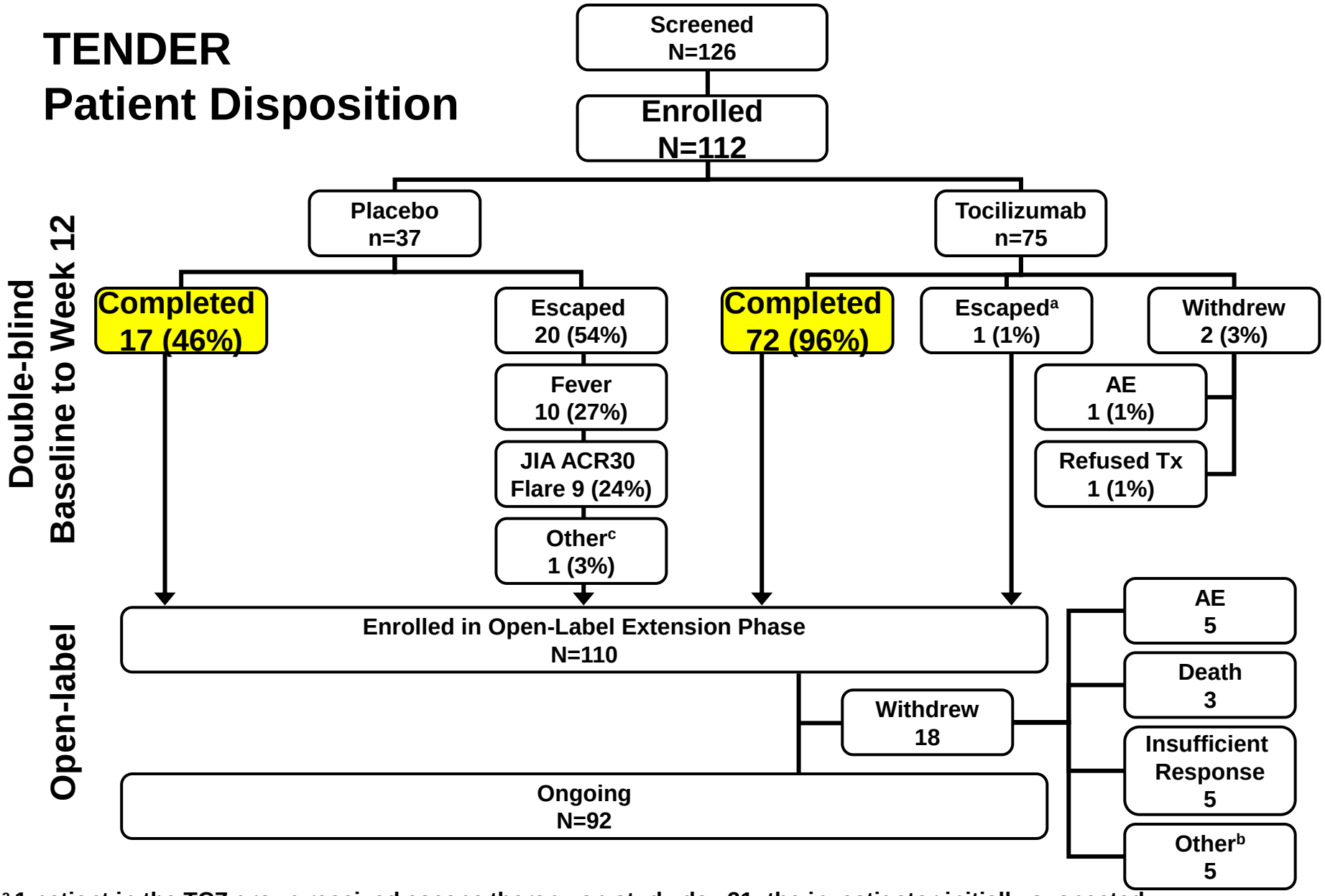
De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.

TENDER: Demographic and baseline characteristics

	Placebo (N=37)	TCZ (N=75)
Age (y), mean (SD)	9.1 (4.4)	10.0 (4.6)
Disease duration, mean (SD)	5.1 (4.4)	5.2 (4.0)
No. of previous DMARDs mean (SD)	1.4 (1.4)	1.3 (1.1)
Previous IL-1 inhibitor, n (%)	13 (35)	41 (55)
Previous anti-TNF, n (%)	26 (70)	55 (73)
Physician VAS, mean (SD)	61.4 (21.1)	69.6 (15.7)
Parent/patient VAS, mean (SD)	56.3 (21.2)	60.3 (23.8)
No. of active joints, mean (SD)	16.9 (12.9)	21.3 (15.9)
No. of joints with LOM, mean (SD)	17.9 (15.9)	20.7 (15.9)
ESR, mean (SD), mm/hour	54.1 (35.4)	57.6 (31.2)
CHAQ, mean (SD)	1.7 (0.8)	1.7 (0.8)
Fever (last 7 days), n (%)	20 (54)	32 (43)
MTX use, n (%)	26 (70)	52 (69)
Corticosteroid dose, (mg/kg/day PDN eq), mean (SD)	0.27 (0.17)	0.29 (0.18)

Roche: data on file.

TENDER
Patient Disposition



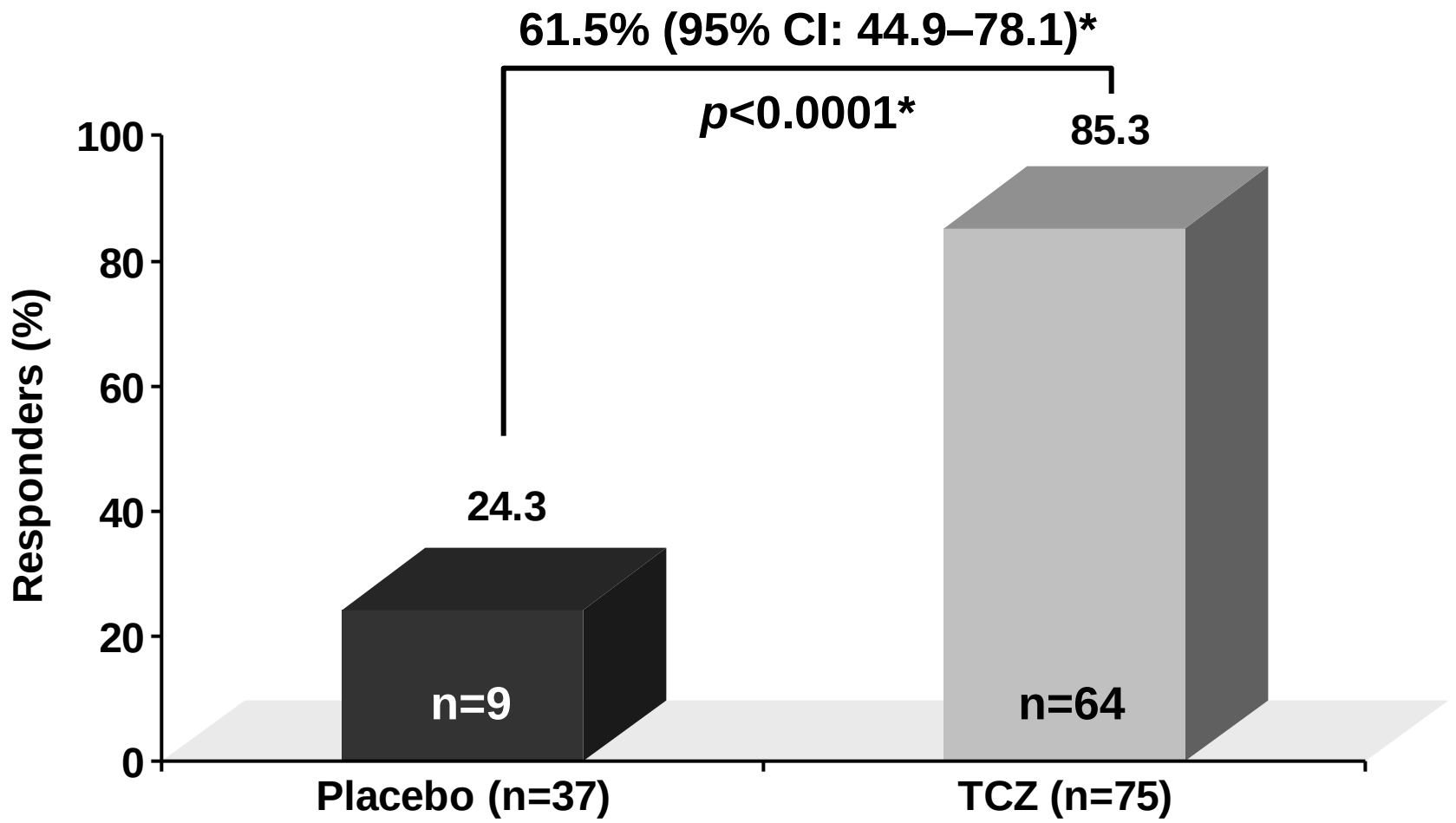
[a] 1 patient in the TCZ group received escape therapy on study day 31; the investigator initially suspected MAS, which was later determined to be liver function test elevations.

[b] 3 patients refused treatment, and 1 patient did not return.

[c] Patient was initially suspected to have MAS, which was later determined to be an sJIA flare.

TENDER: Primary endpoint

JIA ACR30 + Absence of fever at Week 12 (ITT Population)

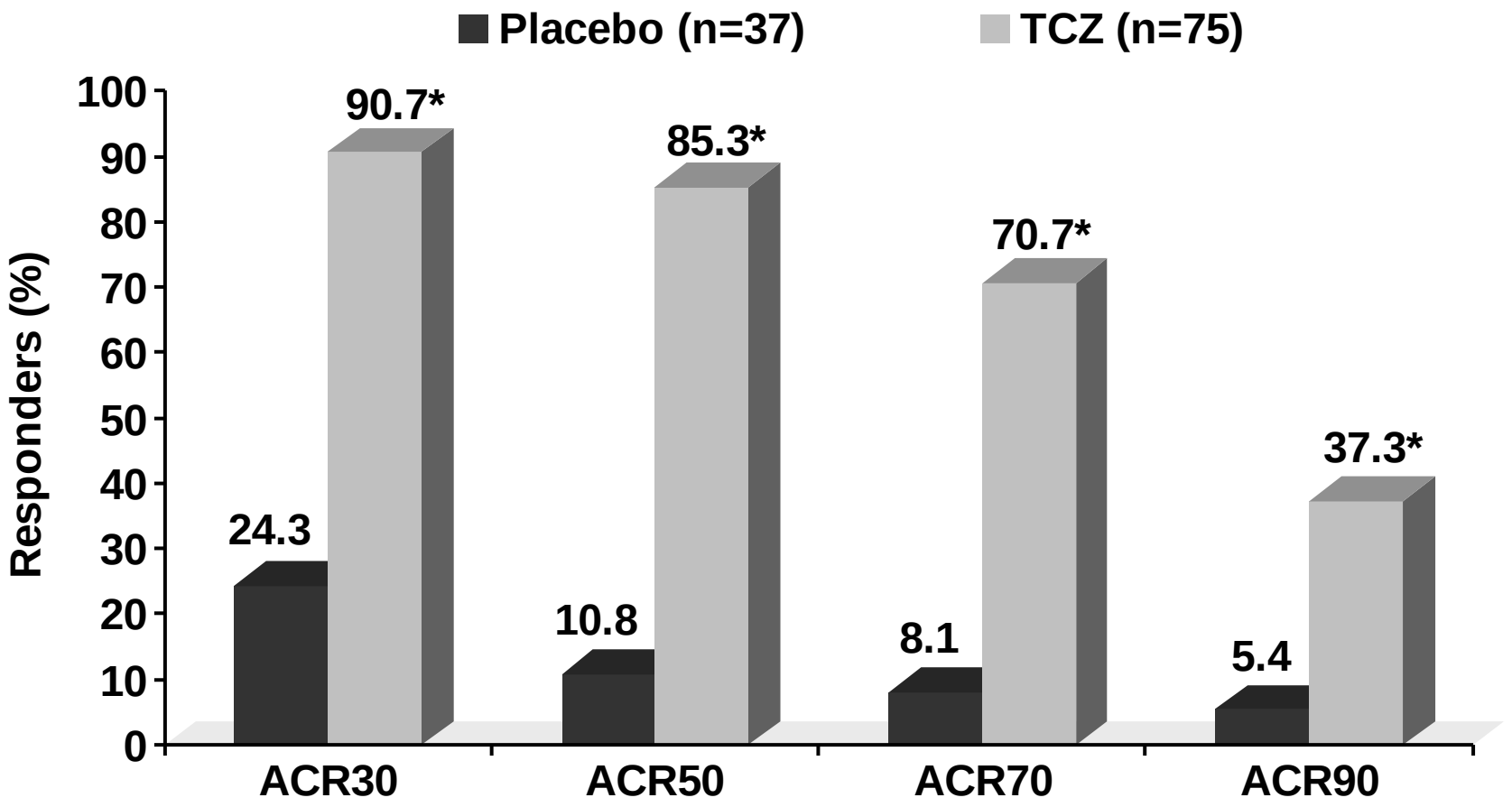


* Weighted difference; Cochran-Mantel-Haenszel analysis adjusted for randomization stratification factors applied at baseline

De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.

TENDER: Secondary endpoints

JIA ACR responses at Week 12 (ITT Population)



*p<0.0001 Cochran-Mantel-Haenszel analysis adjusted for randomization stratification factors applied at baseline

De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.
Roche: data on file.

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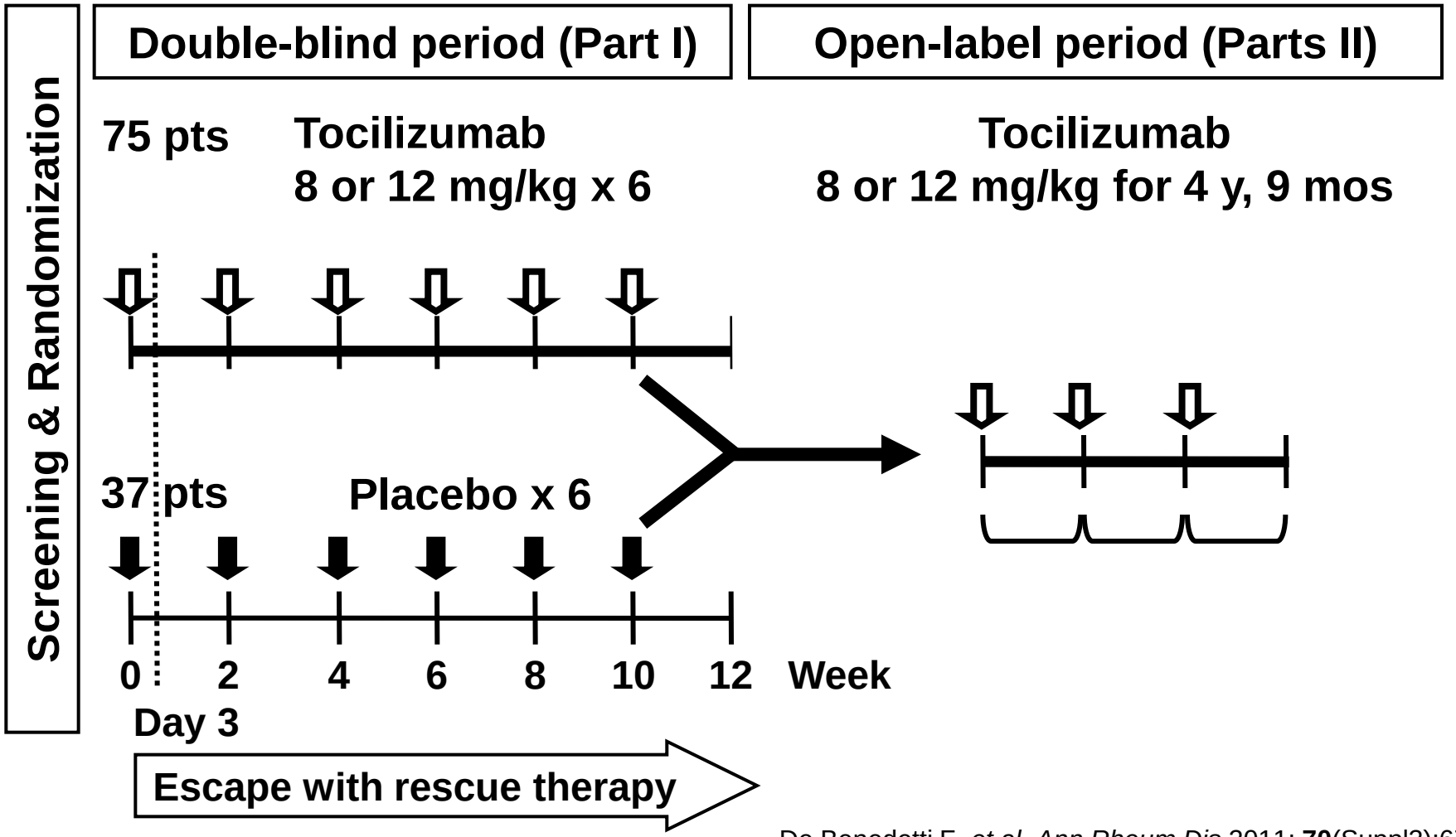
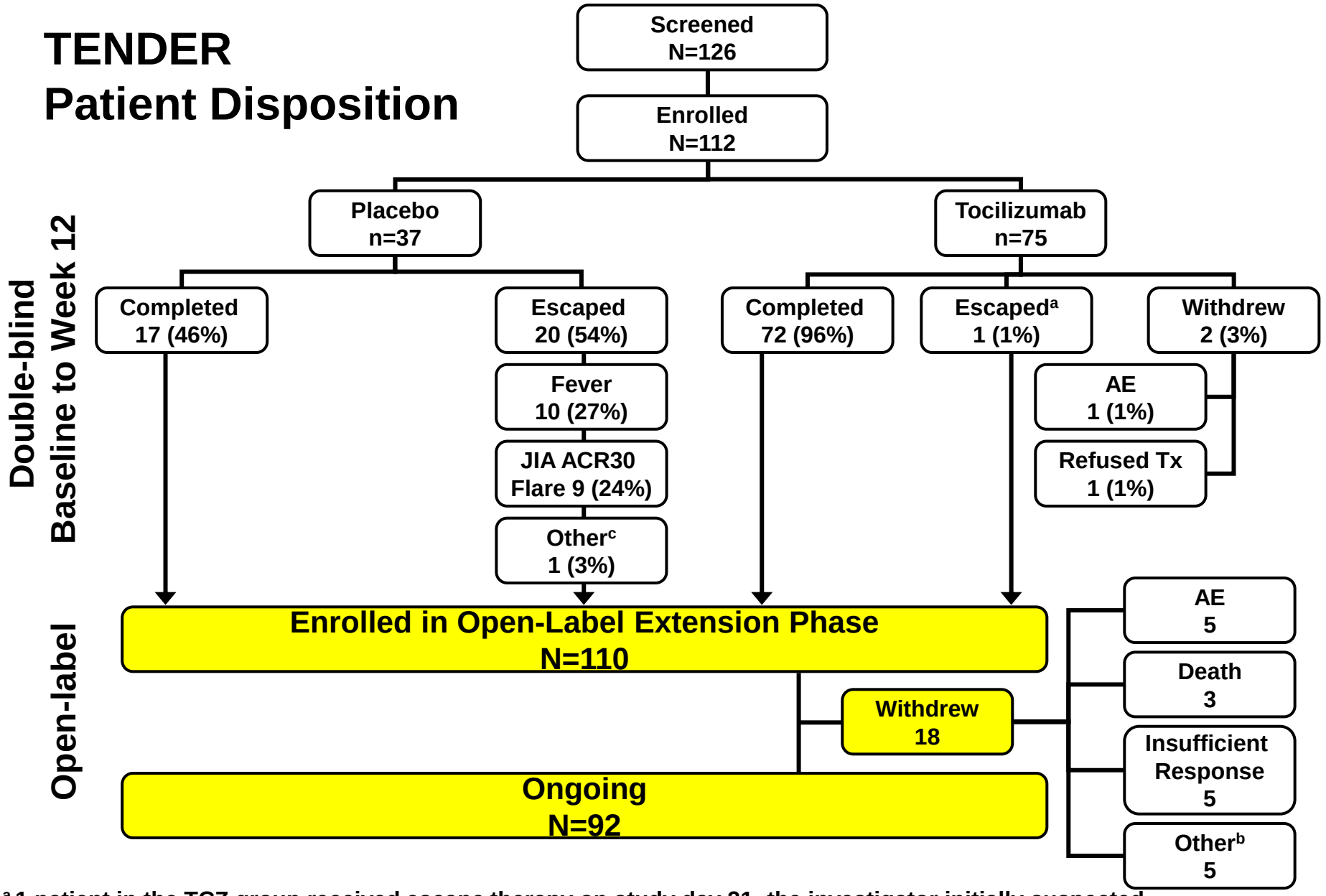
Study Design



De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.

TENDER
Patient Disposition



[a] 1 patient in the TCZ group received escape therapy on study day 31; the investigator initially suspected MAS, which was later determined to be liver function test elevations.

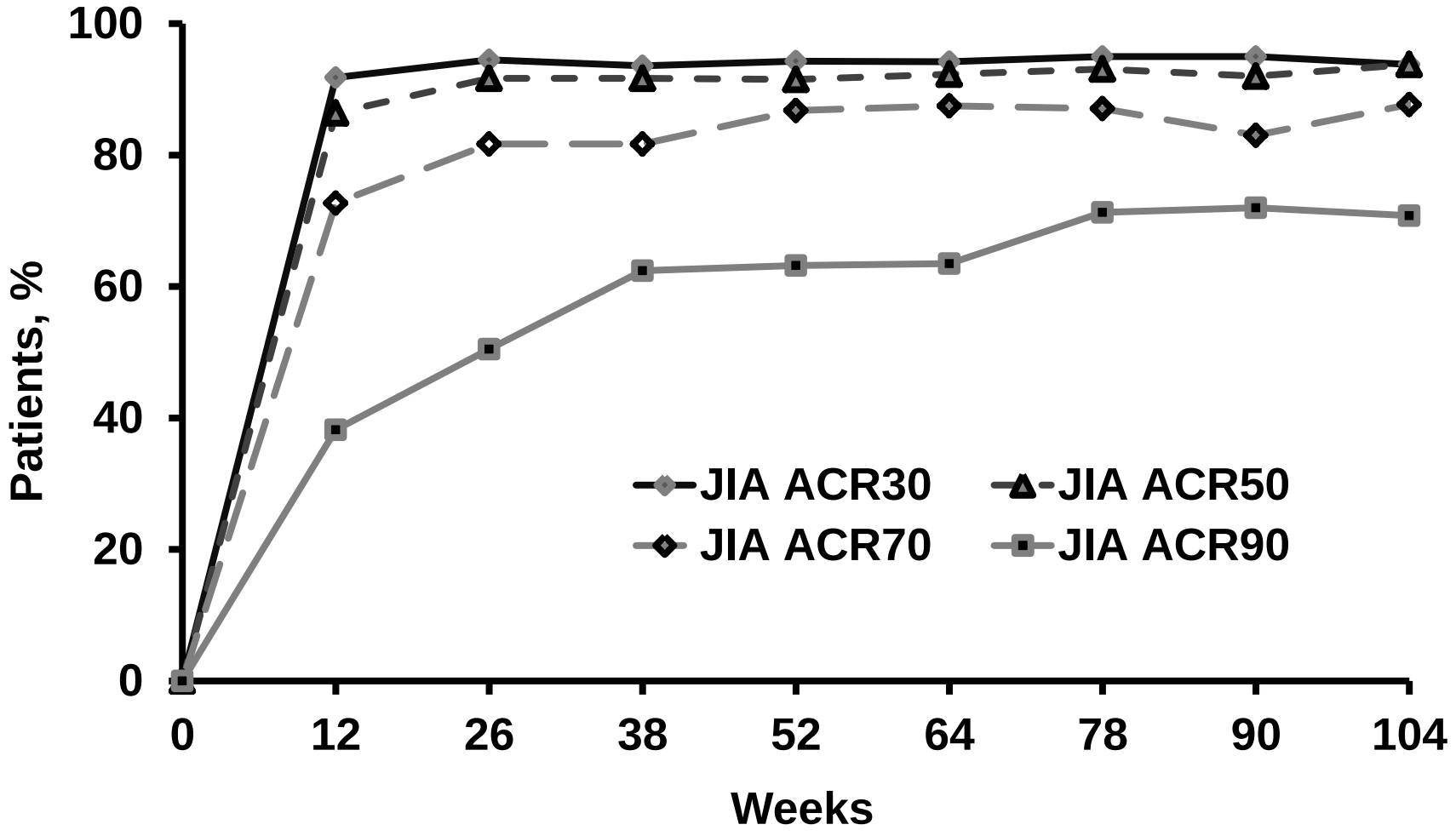
[b] 3 patients refused treatment, and 1 patient did not return.

[c] Patient was initially suspected to have MAS, which was later determined to be an sJIA flare.

TENDER: Analyses of 104-Week Data

- **Baseline**
  - **Patients randomized to TCZ → day 1**
  - **Patients randomized to placebo were re-baselined at the first TCZ dose**
- **Endpoints**
  - **Durability and magnitude of TCZ efficacy response**
  - **Effect of TCZ to reduce or eliminate oral corticosteroids**
  - **Safety of TCZ in chronic administration**
- **Analysis population**
  - **61 patients received at least 104 weeks of TCZ treatment**
  - **Patients who withdrew because of insufficient therapeutic response before week 104 were included and considered nonresponders (n=5) for JIA ACR responses**
  - **Patients who withdrew for nonefficacy-related reasons were excluded (n=15 [9 safety and 6 other]) for JIA ACR responses**

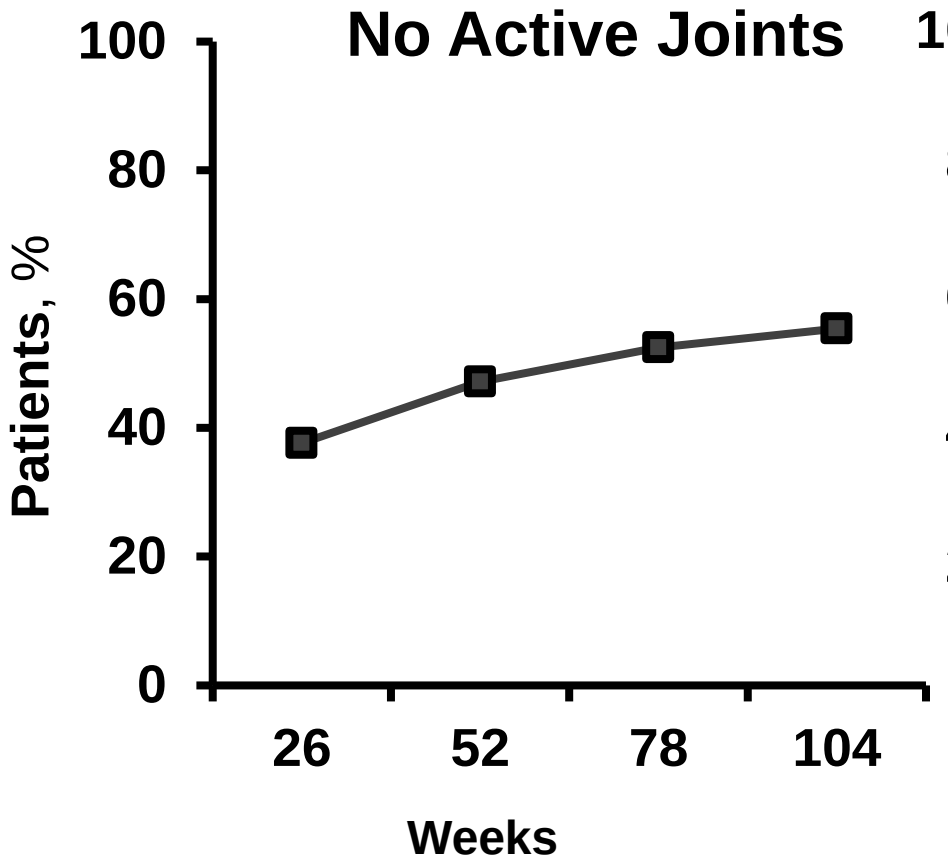
JIA ACR Responses Over Time

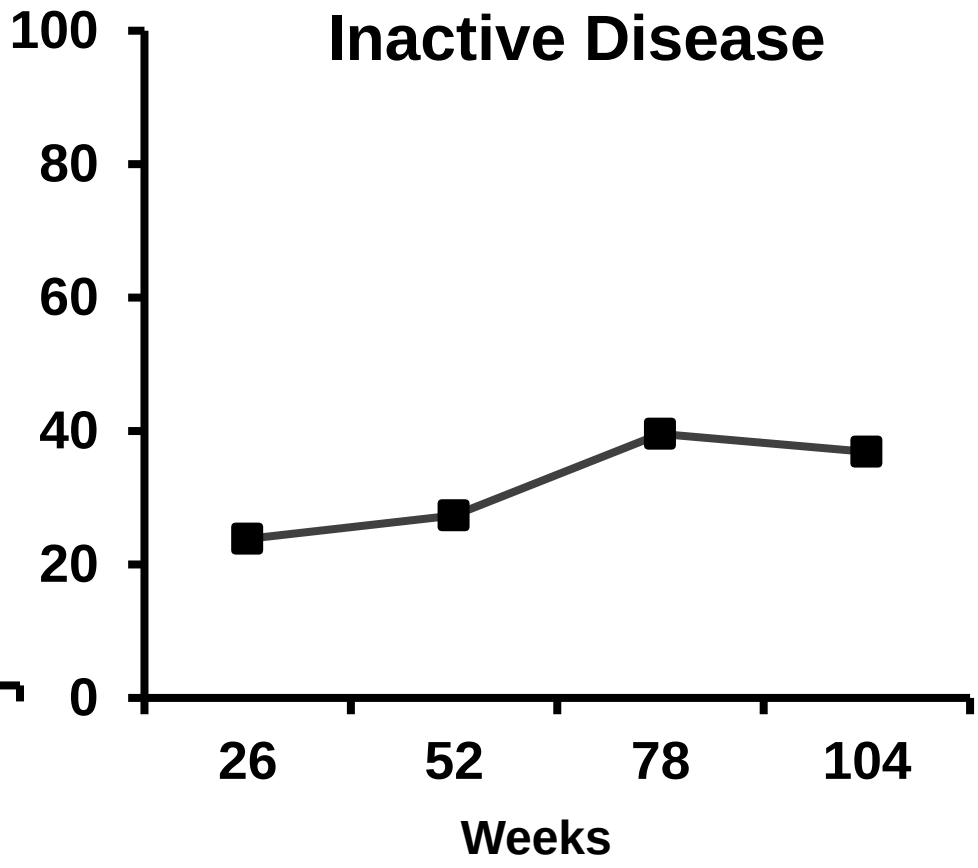


n =	112	110	109	109	106	104	101	100	65

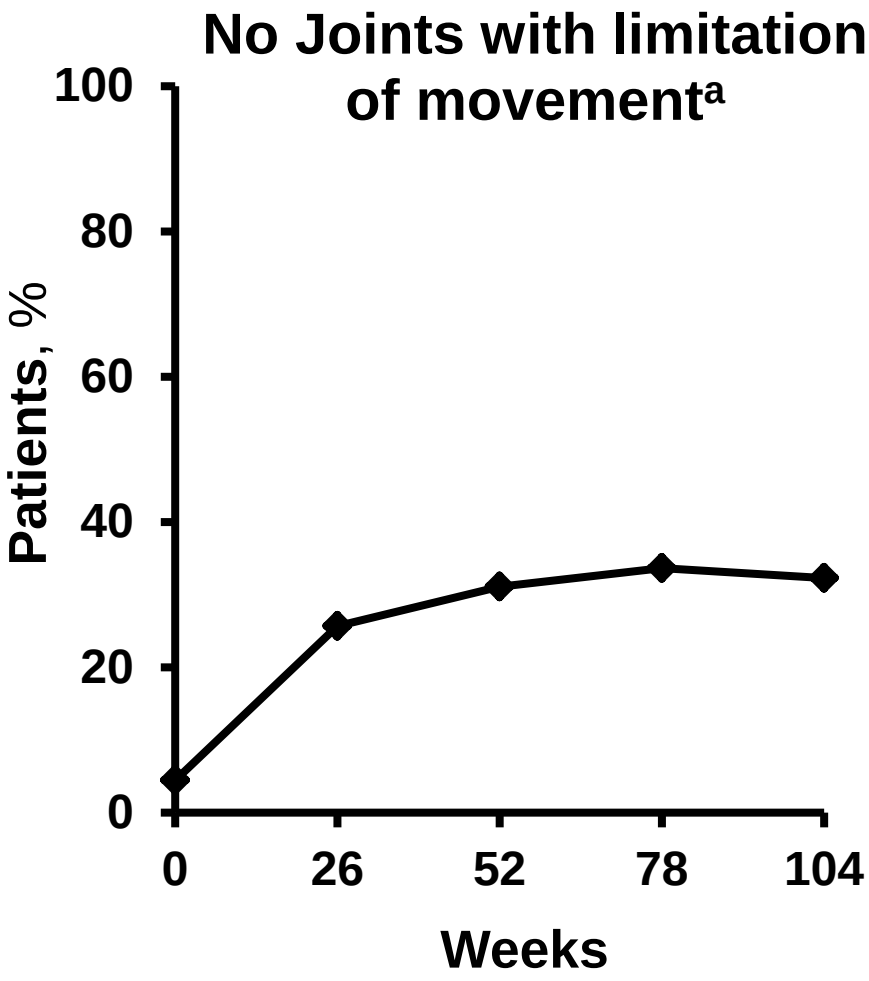
Percentage is based on number of patients who reached time point + patients who withdrew because of insufficient therapeutic response and are assumed to have been nonresponders.

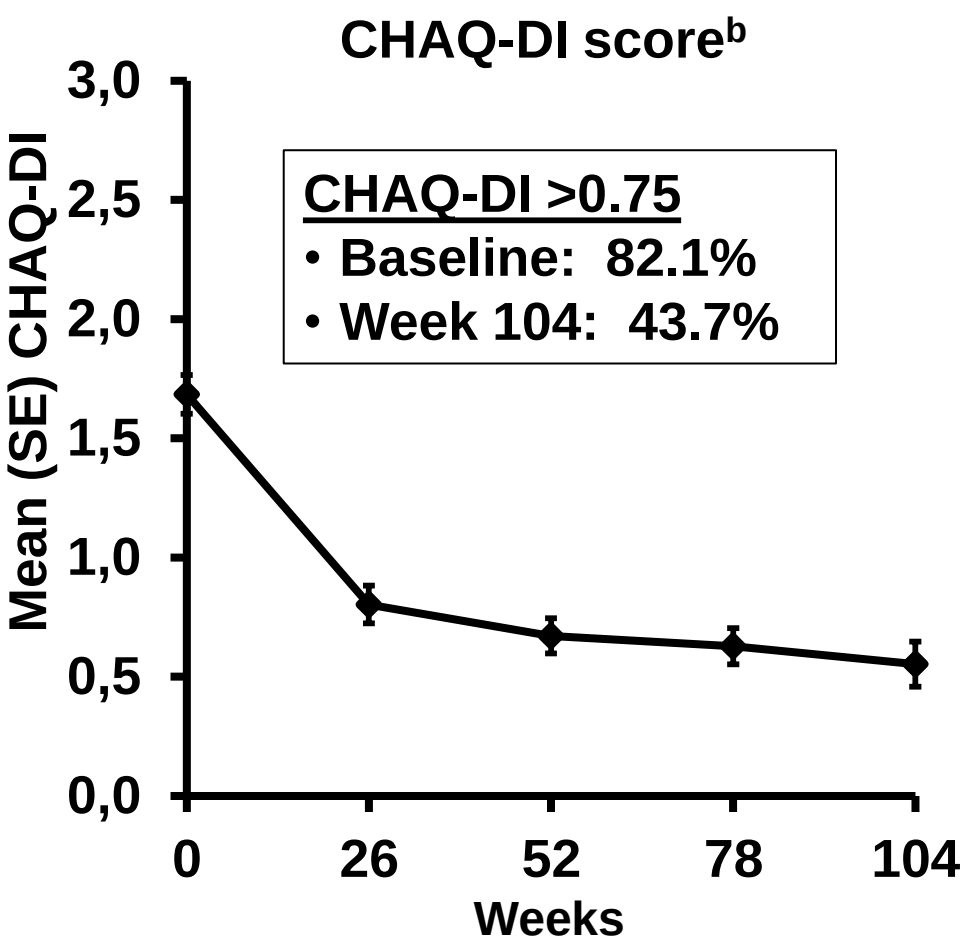
No Active Joints and Inactive Disease Over Time





Physical Function Over Time

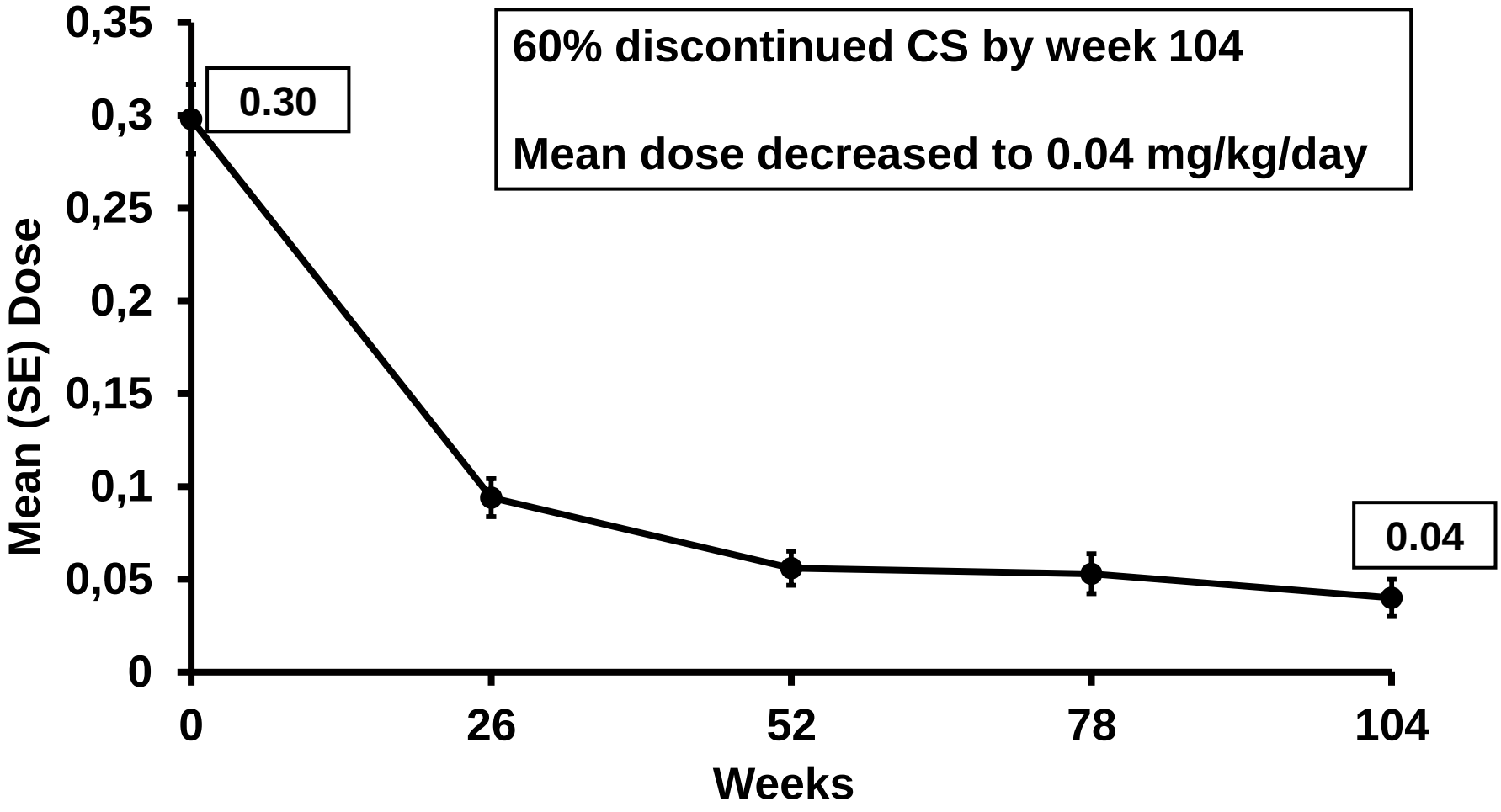




[a]Patients who withdrew because of insufficient therapeutic response are assumed to be nonresponders.

[b]Patients who withdrew are excluded.

Mean Oral Corticosteroid Dose Over Time



Patients who withdrew have been excluded at postwithdrawal visits.

TENDER: Summary of efficacy at Week 104

- **Year 2 results from this global phase III study demonstrated that TCZ was highly effective for the treatment of sJIA**
  - **Efficacy is sustained over time**
  - **60% of patients achieved an ACR90 response**
  - **50% of patients had no active joints**
  - **37% of patients met inactive disease criteria**
  - **60% of patients discontinued corticosteroids**

De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.
Roche: data on file.

TENDER: Analyses of 104-week safety data

- **All randomized patients who received 1 or more doses of TCZ**
- **Includes the full-exposure data for each patient**
- **Individual patient exposures to TCZ varies depending on the date of first TCZ infusion to the last data cut or withdrawal**

Roche: data on file.

Cumulative Safety at week 104

	Prior Safety Update[a]	Week 104[b]
Exposure to TCZ, y	157.46	202.03
Rate of SAEs/100PY (n)	24.8 (39)	23.3 (47)
Rate of infections/100PY (n)	303.6 (435)	282.1 (570)
Rate of serious infection AEs/100PY (n)	11.4 (18)	10.9 (22)
SAEs related (remotely, possibly, probably) to TCZ/100 PY (n)	8.3 (13)	7.4 (15)
Macrophage activation syndrome/100PY (n)	1.9 (3)	1.5 (3)
AEs leading to withdrawal/100PY (n)	3.8 (6)	3.0 (6)
Deaths/100PY (n)	0.6 (1)	1.5 (3)

[a]Includes all safety data in the database up to and including August 10, 2010.
[b]Includes all safety data in the database up to the week 104 infusion (based on date of randomization) for each pt. The last date for this was May 31, 2011.

Most Common* Serious Adverse Events

Event, n (%)	N = 112
Varicella	4 (3.6)
Gastroenteritis	4 (3.6)
Macrophage activation syndrome	3 (2.7)
Pneumonia	3 (2.7)
Dehydration	2 (1.8)
Herpes zoster	2 (1.8)

*Preferred terms with incidence > 1 patient

TENDER: AEs leading to withdrawal

	N=112
AEs leading to withdrawal, n	6
Angio-oedema	1
Transaminase increase[a]	2
Pulmonary veno-occlusive disease	1
Panniculitis	1
Macrophage activation syndrome	1

[a]Withdrawal per protocol

Roche: data on file.

Cumulative Safety at week 104

	Prior Safety Update	Week 104 (b)
Exposure to TCZ, y	157.46	202.03
Rate of SAEs/100PY (n)	24.8 (39)	23.3 (47)
Rate of serious infection AEs/100PY (n)	11.4 (18)	10.9 (22)
SAEs related (remotely, possibly, probably) to TCZ/100 PY (n)	8.3 (13)	7.4 (15)
Deaths/100PY (n)	0.6 (1)	1.5 (3)
Pneumothorax	1	1(c)
Sepsis (possibly related)		1 (d)
Road Traffic Accident		1 (e)

(b) Includes all safety data in the database up to the week 104 infusion (based on date of randomization) for each pt. The last date for this was May 31, 2011.
(c) Male patient age 16 y with disease of long duration and severe stunted growth who achieved JIA ACR90 response. Death was due to suspected tension pneumothorax at week 52 and was considered unrelated to study drug.
(d) road accident reported as unrelated
(e) sepsis, streptococcus cultured post-mortem from blood and stools

Mortality in systemic JIA

Retrospective studies (including also monocyclic and polycyclic patients)

- **2 /80 (Lomater ,J Rheumatol 2000)**
- **2 /111 (Spiegel, A&R 2000)**
- **8/182 (Russo, PRES meeting 2001)**

Deaths after discontinuation from TENDER

Pat #	Country	Event name	Age at death	Date of Death (duration from last TCZ dose)	Duration of TCZ tx	Date of last TCZ dose	Reason for withdrawal from TENDER
1531*	Netherlands	Death of unknown cause	13 y 3 mo.	July-10 (6 mo.)	50 wks	Jan-21-10	Insufficient therapeutic response
1611	Italy	Atrioventricular block (in hyperkalaemia)	17 y 9 mo.	Dec-11-10 (1 y 1 mo.)	54 wks	Nov-18-09	AE - Pulmonary veno-occlusive disease
1634	Italy	Cardiac arrest	18 y 7 mo.	Apr-15-11 (1 y 2 mo.)	48 wks	Feb-01-10	Insufficient therapeutic response

*** Patient 1531 entered another biologic study April 2010.**

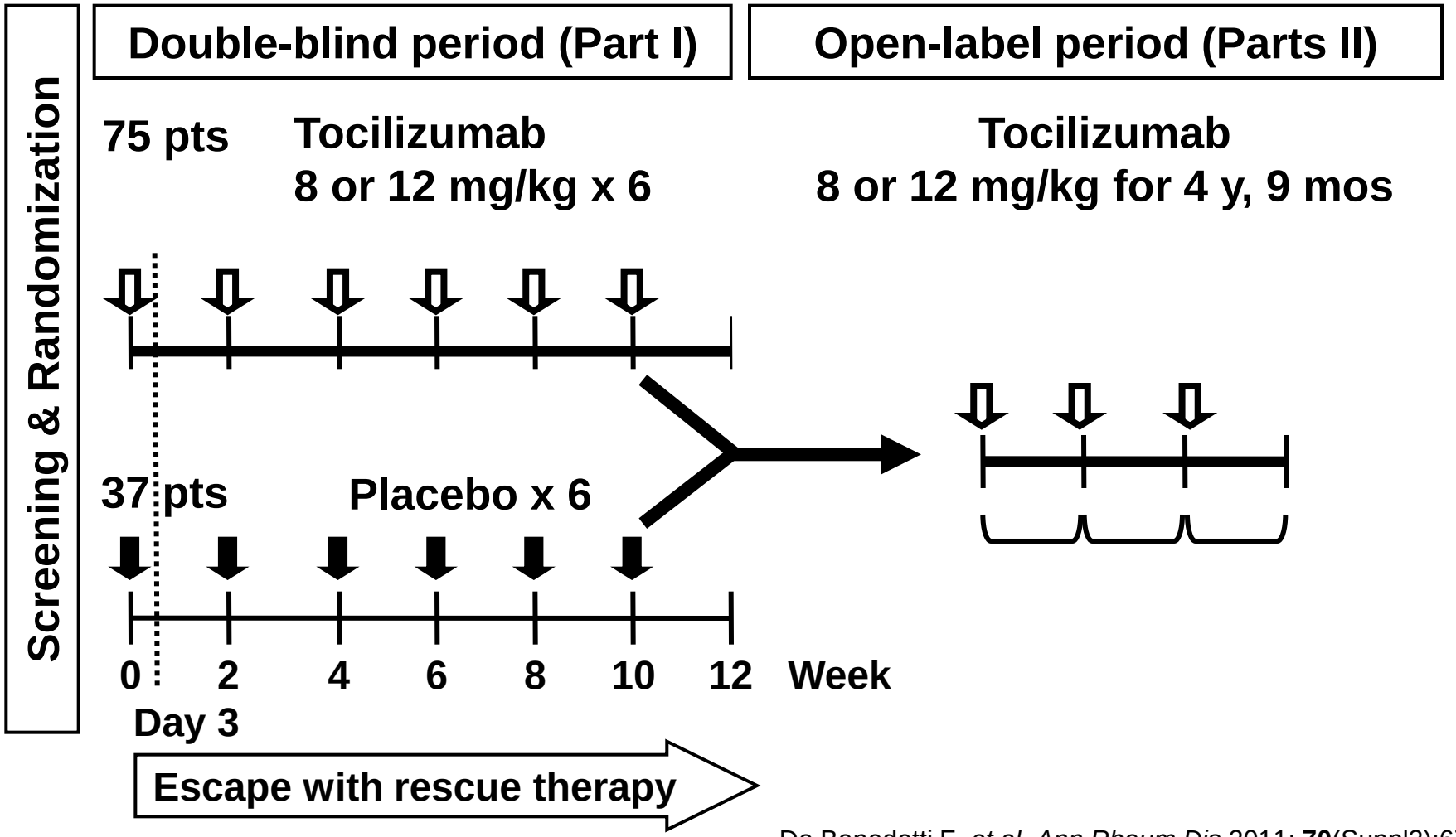
TENDER: Clinical Laboratory Evaluations

	Grade[a]	No. (%)
Neutrophils	3 (500-<1,000 cells/mm^3)	26 (23.2)
	4 (<500 cells/mm^3)	2 (1.8)[b]
Platelets	3 (25,000-<50,000 cells/mm^3)	1 (0.9)[c]
	4 (<25,000 cells/mm^3)	0
ALT	3 (>5-20 x ULN)	9 (8.0)
	4 (>20 x ULN)	1 (0.9)[c]

[a] Common Toxicity Criteria Vers. 3 Grades.
[b] Both single occurrences, returned to normal no associated infection.
[c] Platelet decrease and ALT increase occurred during MAS.

TENDER: A 12-week randomized, double-blind, placebo-controlled, parallel group, 2-arm study (Part I) with a 5-year single arm open-label extension (Parts II)

Study Design



De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.

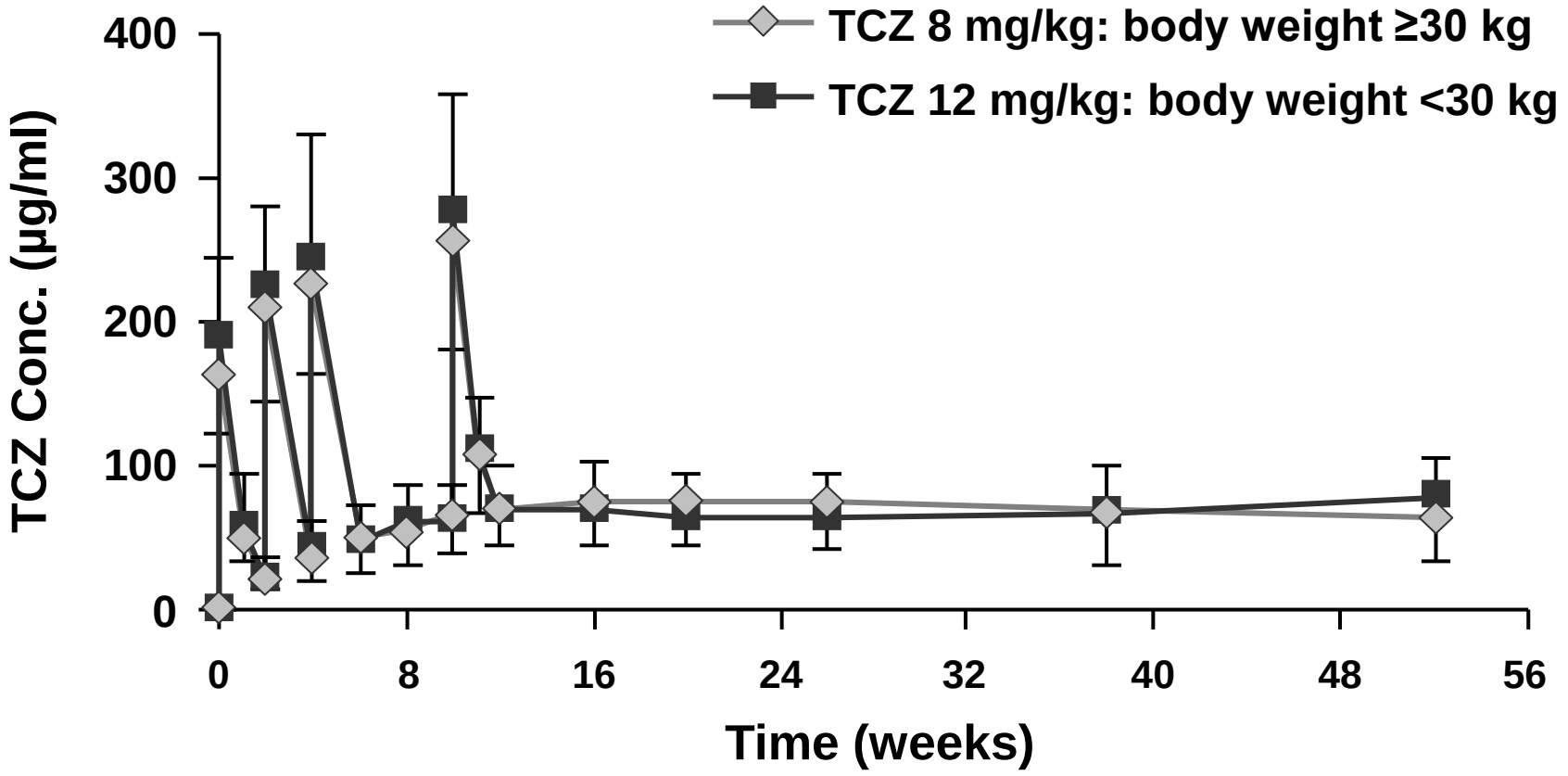
TENDER: TCZ dosing regimen

- **Decreased efficacy associated with a trend for lower exposure to TCZ was observed in sJIA children with lower body weight**
- **Based on PK modeling of data from 56 children with sJIA**
- **TCZ administered i.v. every 2 weeks, dosed by baseline body weight**
  - **12 mg/kg for children body weight <30 kg every 2 weeks**
  - **8 mg/kg for children body weight ≥30 kg every 2 weeks**

Roche: data on file.

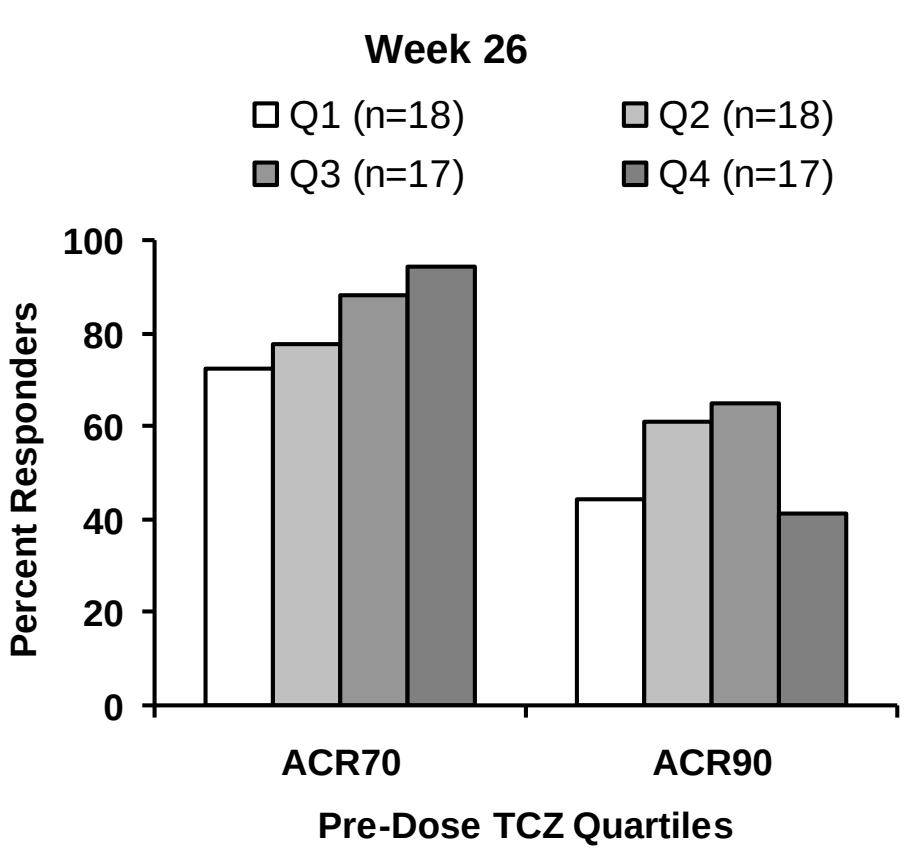
TENDER: PK results (week 52)

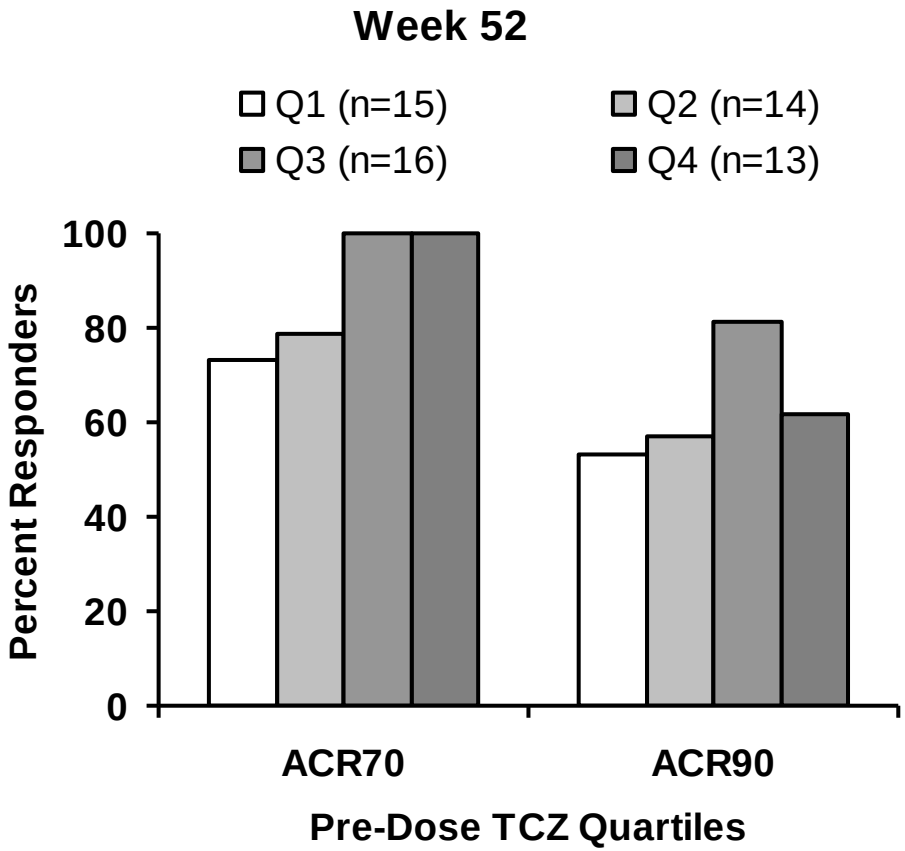
Comparable exposure between 2 dosing regimens
Mean (±SD) Concentration-Time Profile



Zhang X, *et al.* EULAR 2011 Poster FRI0200.

TENDER: JIA ACR70 and ACR90 responders by Pre-Dose TCZ Serum Concentration Quartiles





Roche: data on file

TENDER: Neutropenia at week 52

- **Higher frequency of neutropenia compared to adults**
- **No association with infections**
- **No association with exposure**

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
C min (µg/mL) Week 52	N=26	N=2	N=16	N=14	N=0
	65.0 ±29.5	71.3 ±33.9	83.8 ±31.3	62.2 ±28.1	-

Roche: data on file

TENDER: PK conclusion (week 52)

- **Comparable exposure between 2 dosing regimens**
- **No association of exposure with efficacy**
- **No association of exposure with safety**

Zhang X, *et al.* EULAR 2011 Poster FRI0200.

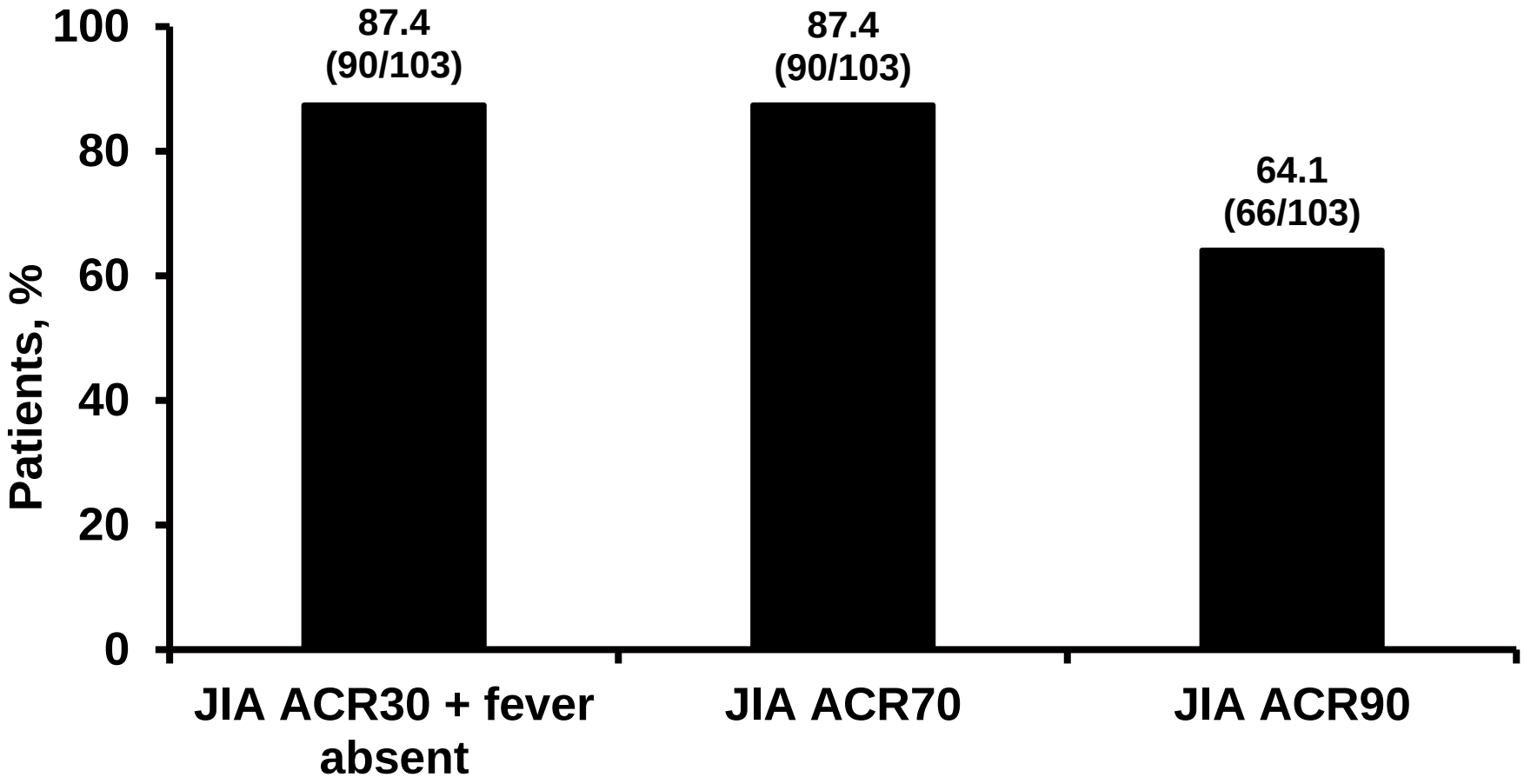
sJIA: Clinical And Prognostic Heterogeneity

1. **Persistent versus monocyclic versus polycyclic course**

2. **Response to anakinra**
   - **Early in disease course**
   - **Low number of active joints**

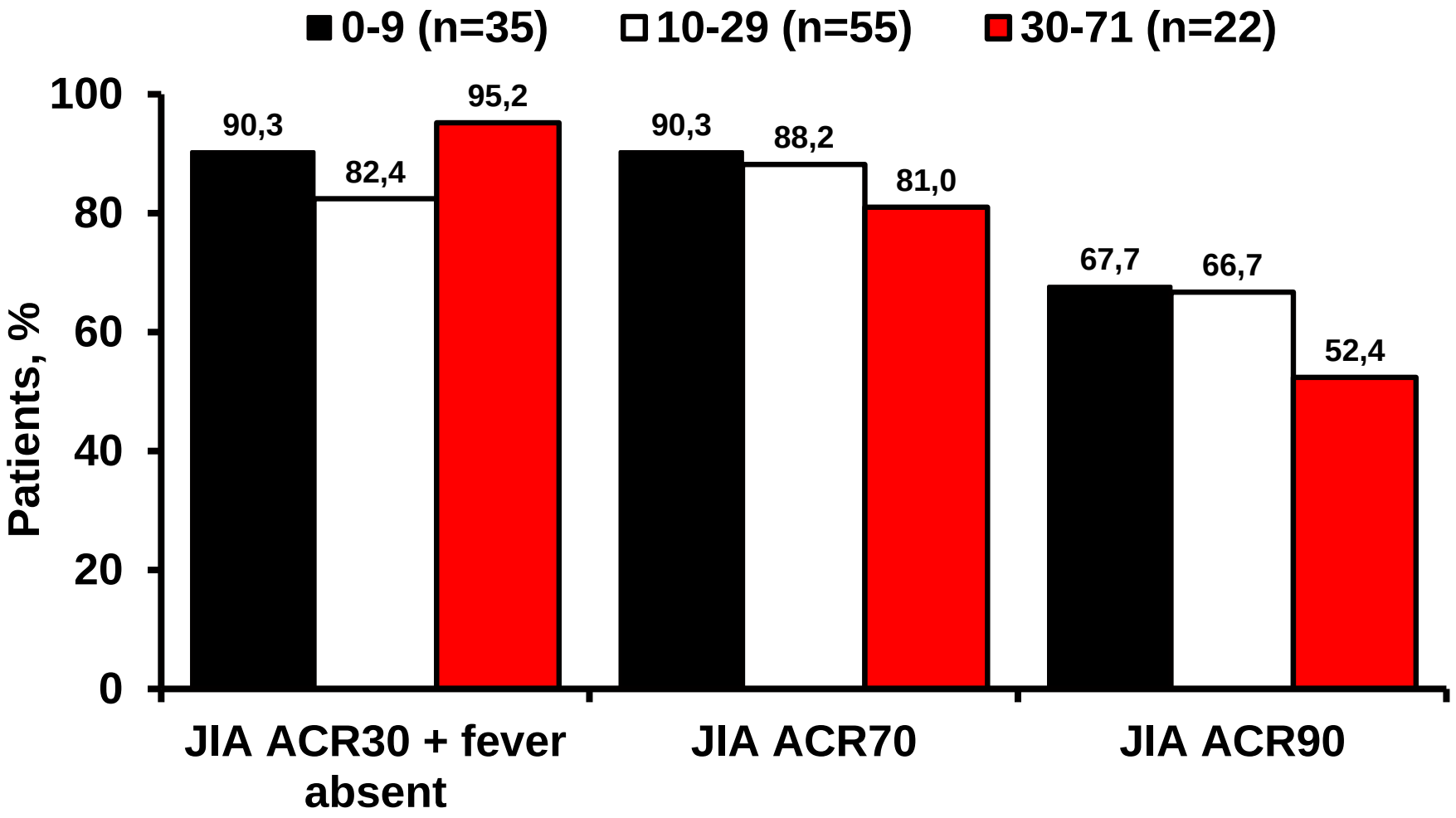
Cassidy et al *J Clin Invest* 1973; Spiegel LR *Arthritis Rheum* 2000; Modesto C *Clin Exp Rheumatol* 2001; Singh-Grewal D *Arthritis Rheum* 2006; Sandborg C *J Rheumatol* 2006; Bloom BJ *J Rheumatol* 2009; Gattorno M *Arthritis Rheum* 2008; Nigrovich *Arthritis Rheum* 2011.

TENDER: Overall Response at Week 52

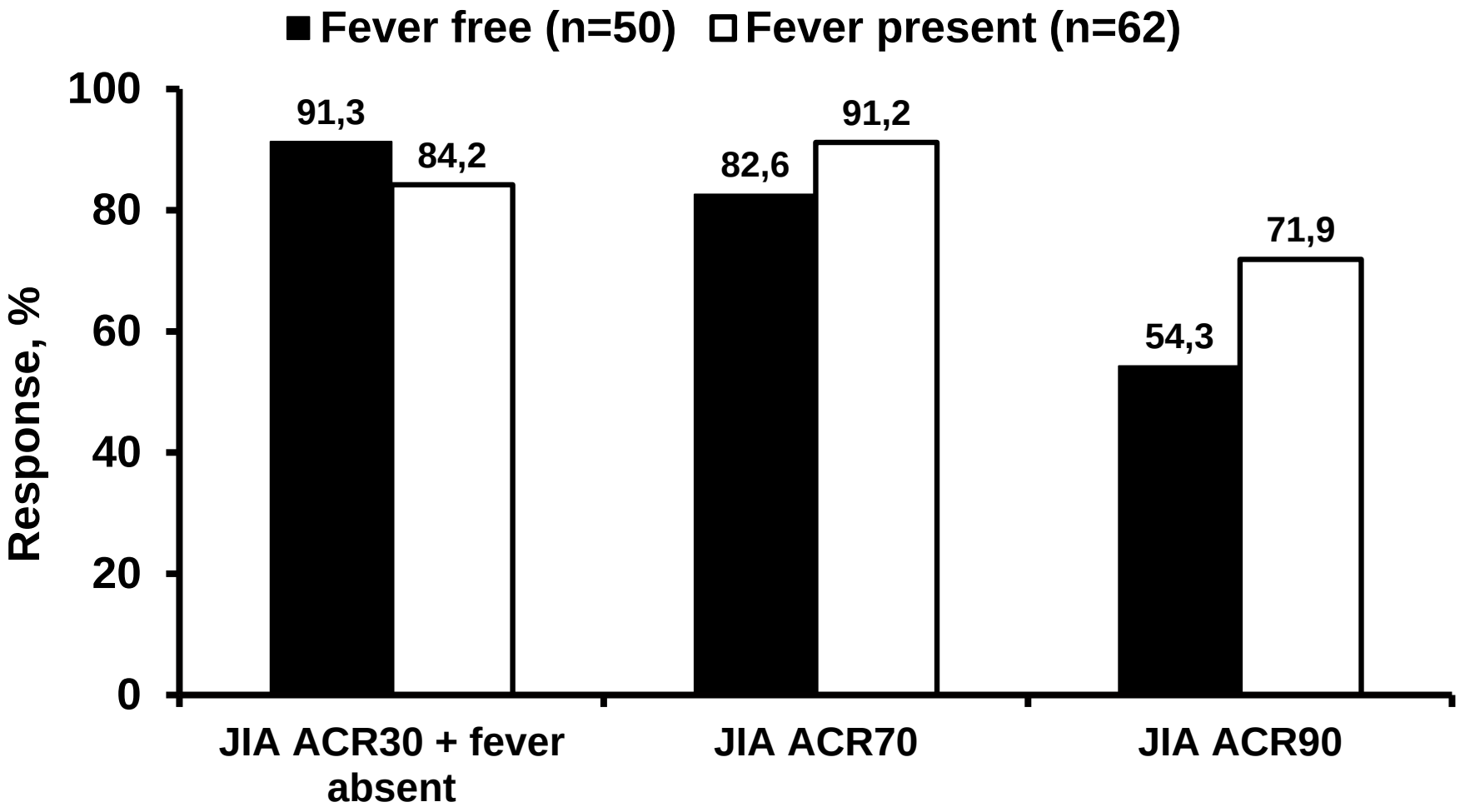


Absence of fever: no temperature > 37.5°C in the preceding 7 days.
Percentage based on no. of patients reaching week 52 visit + no. of patients who withdrew due to insufficient response.

Response by Number of Active Joints at Baseline

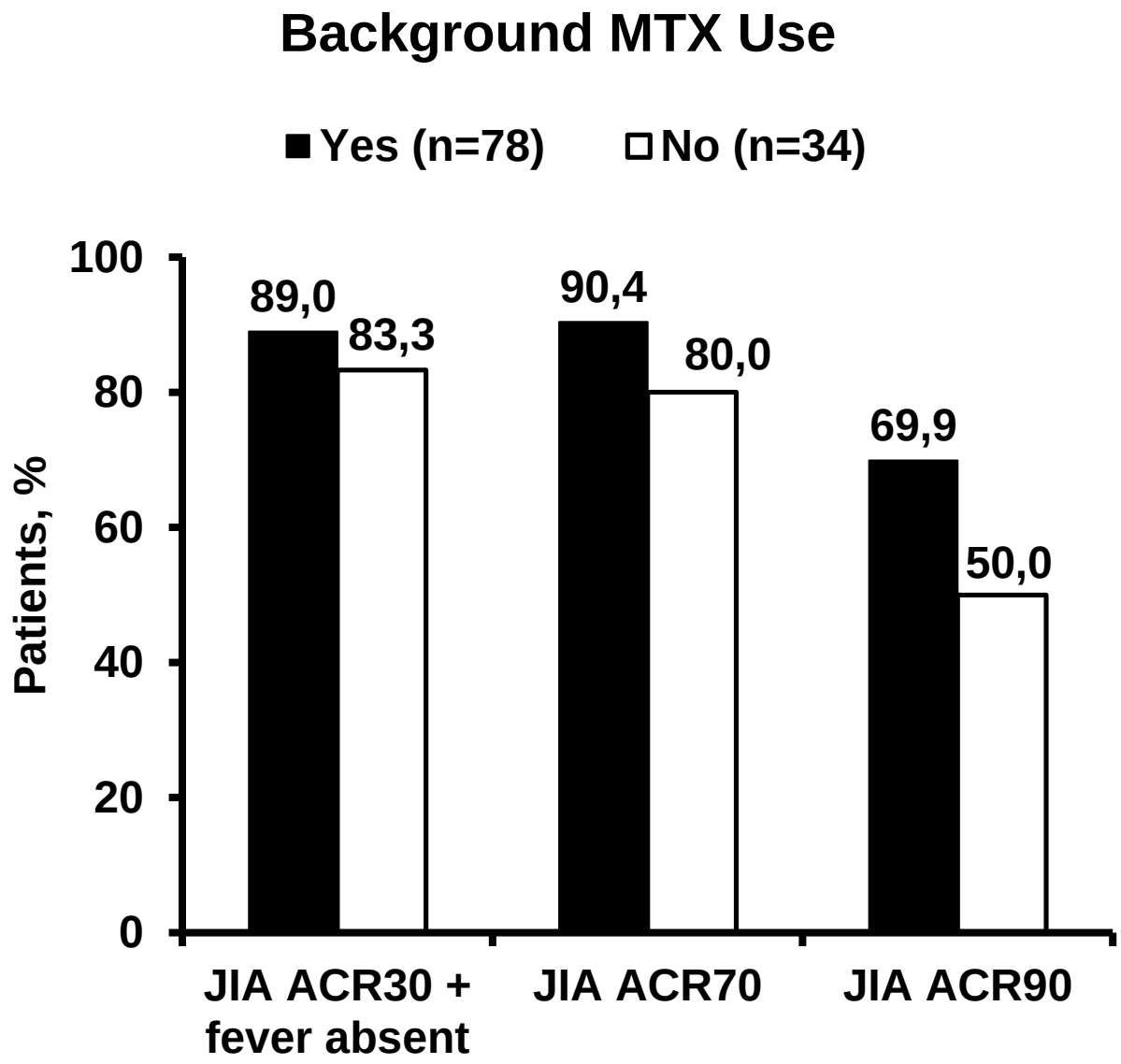


Response by Fever Status at Baseline



Presence of fever: any temperature ≥ 37.5°C in the preceding 7 days.
Fever at baseline: any temperature ≥ 37.5°C in the 14 days preceding the baseline visit.

Response by background use of MTX



- **Role in systemic and local inflammatory responses**
  - **Unique biology of the soluble IL-6 receptor**
  - **Role in mononuclear cell recruitment**
- **IL-6 as target in s-JIA**
  - **The rational and the use of anti-IL-6 Tx as a probe for proof of concept**
- **Anti-IL-6 treatment in s-JIA**
  - **2 year data from TENDER with TCZ : efficacy, safety**
  - **1 year: PK; response according to baseline disease characteristics**
- **IL-1 and IL-6: in vitro and in vivo interplay**

PRCSG
Pediatric Rheumatology Collaborative Study Group

PRINTO
Paediatric Rheumatology INternational Trials Organization

Roche

Investigators
43 centres from
17 countries

Argentina	Cuttica	Espada	Garay		
Australia	Allen	Chaitow	Murray		
Belgium	Joos	Wouters			
Brazil	Silva	Xavier			
Canada	Roth	Schneider			
Czech Republic	Dolezalova				
Germany	Horneff	Huppertz	Minden		
Greece	Mantzourani	Siammopoulou	Vougiouka		
Italy	De Benedetti	Gerloni	Martini	Zulian	
Mexico	Burgos	Maldonado			
Netherlands	Wulffraat				
Norway	Flato				
Poland	Zuber				
Slovakia	Rovensky				
Spain	Calvo	Garcia-Consuegra			
UK	Baildam	Woo			
USA	Brown	Chalom	Jerath	Kimura	Lovell
	Myones	O'Neill	Onel	Spalding	Zemel

- **Role in systemic and local inflammatory responses**
  - **Unique biology of the soluble IL-6 receptor**
  - **Role in mononuclear cell recruitment**
- **IL-6 as target in s-JIA**
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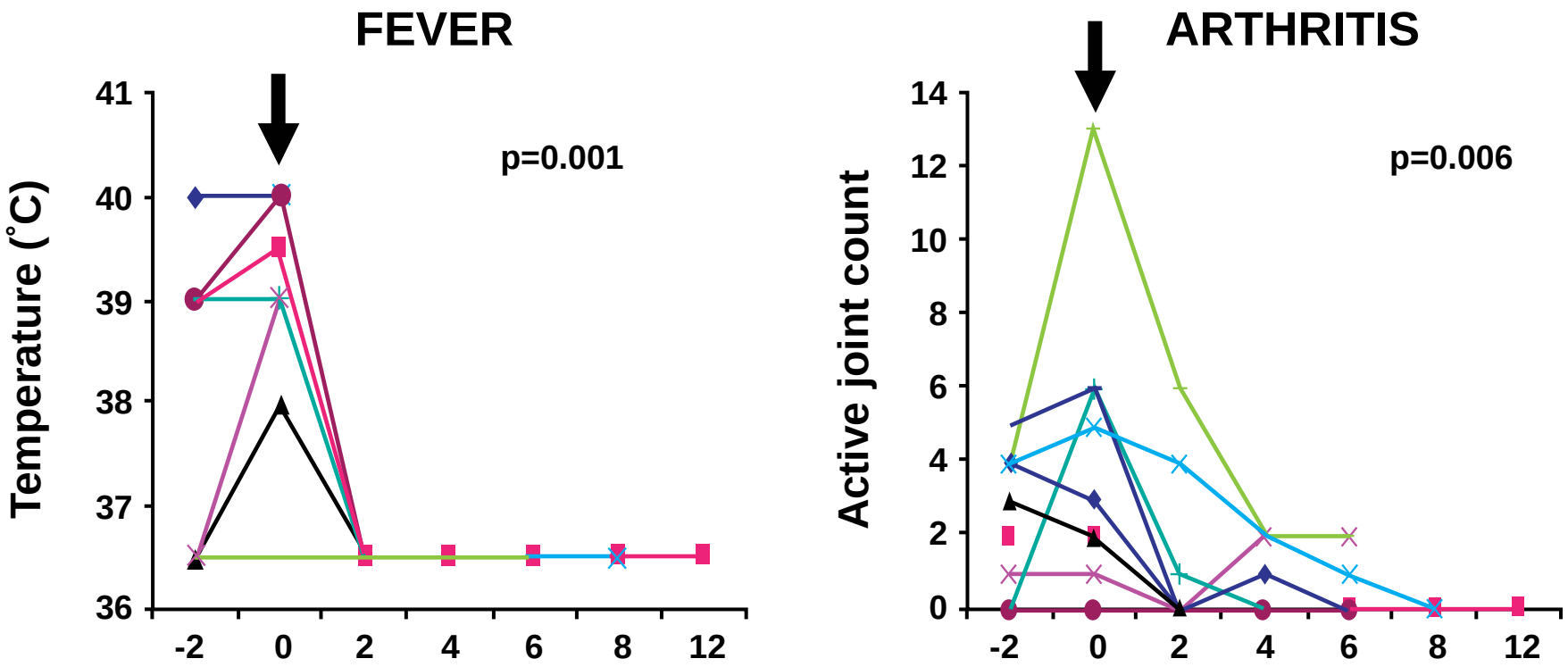
- **Anti-IL-6 treatment in s-JIA**
  - **2 year data from TENDER with TCZ : efficacy, safety**
  - **1 year PK**
- **IL-1 and IL-6: in vitro and in vivo interplay**

Reverse translation identifying the role of IL-1β in sJIA using IL-1 inhibitors

- **Increased expression of IL-1 related genes**
- **Clinical response to anakinra in patients with sJIA**



Coloured lines represent individual sJIA patients
Black arrow indicates time of treatment initiation

Pascual V, *et al. J Exp Med* 2005; **209**:1479–1486

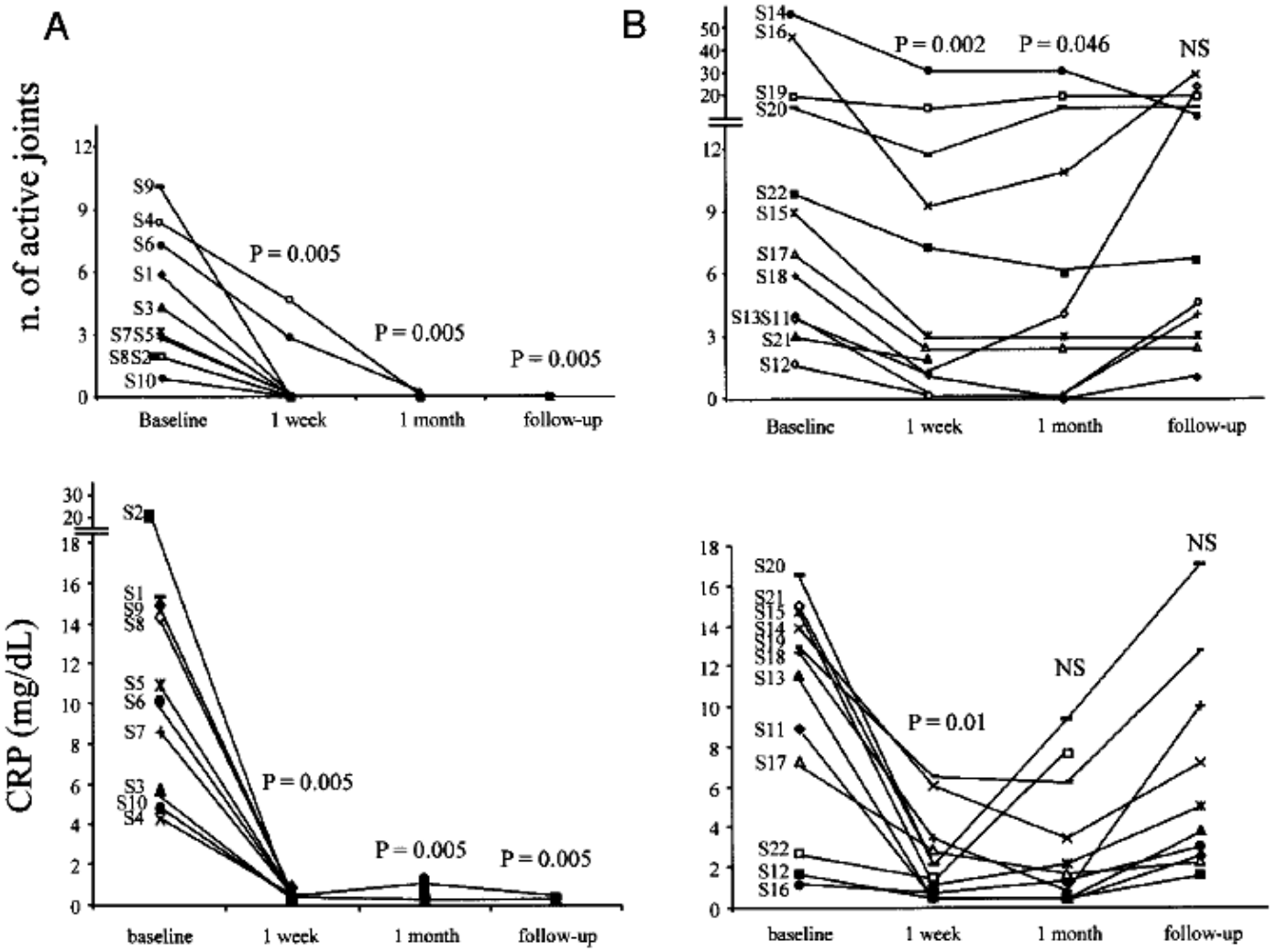
IL-1 inhibition with anakinra in s-JIA

- **Uncontrolled studies**
- **Variable percentage of response (30-70%)**
- **Late versus early treatment**
- **Disease characteristics responders vs non responders**

Lequerré T et al Ann Rheum Dis 2008
Gattorno M et al Arthritis Rheum 2008
Quartier P et al Ann Rheuma Dis 2010
Nigrovich PA et al Arthritis Rheum 2011

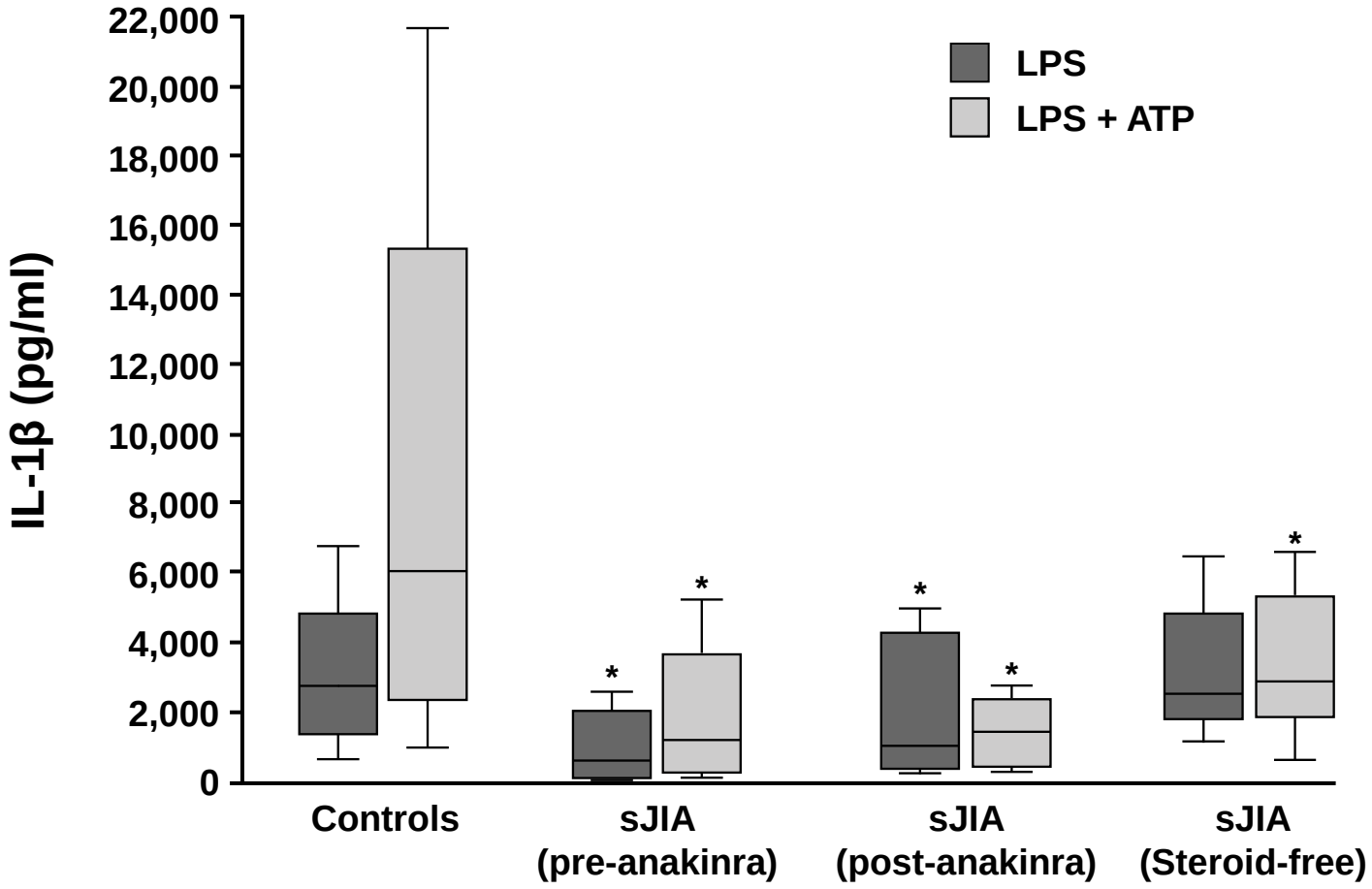
The Pattern of Response to Anti–Interleukin-1 Treatment Distinguishes Two Subsets of Patients With Systemic-Onset Juvenile Idiopathic Arthritis

Gattorno M et al. A&R 2008



Normal IL-1β production following "classical" inflammasome activation

- **Normal production after stimulation with LPS alone**
- **No increase after addition of ATP**

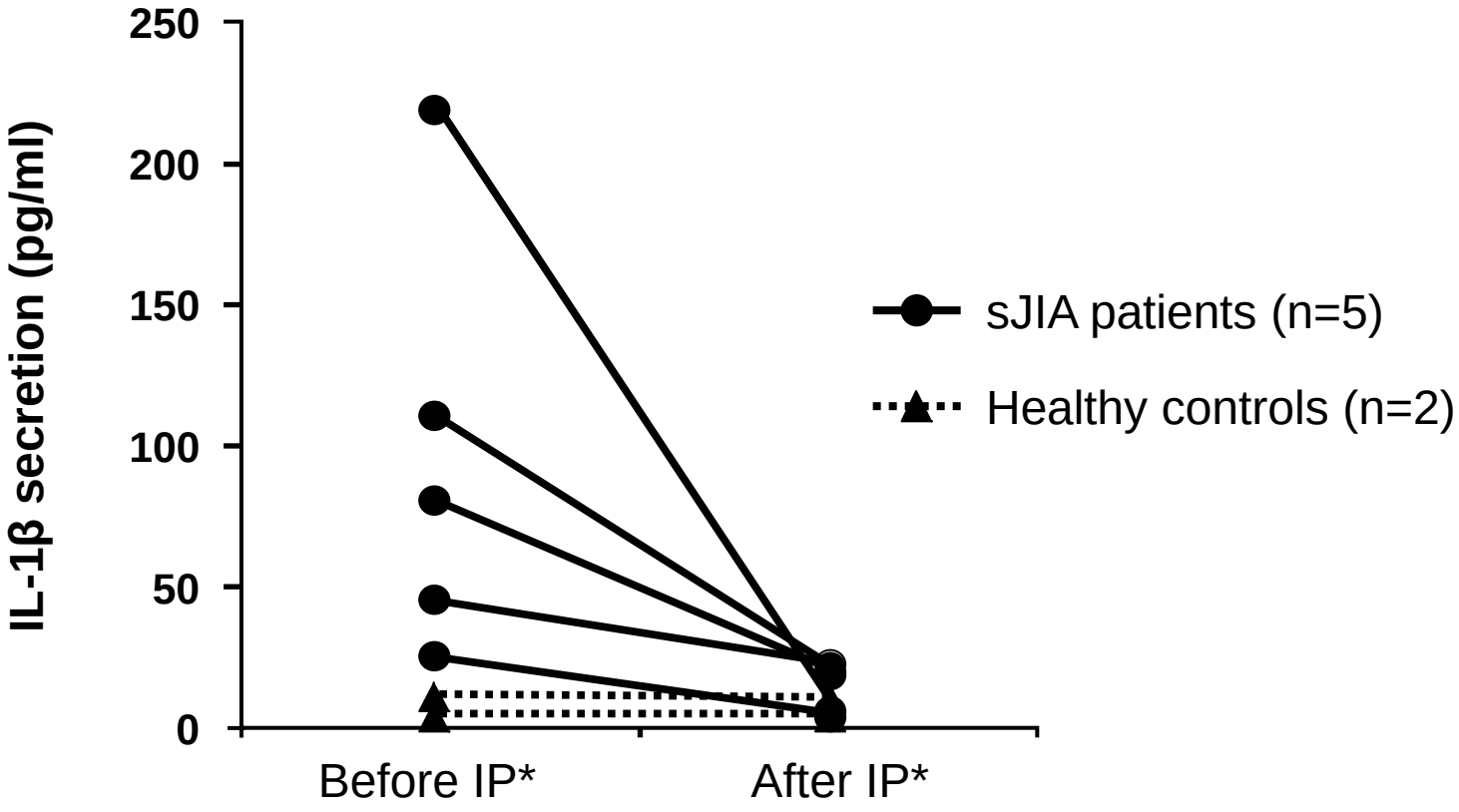


LPS = lipopolysaccharide; ATP = adenosine trisphosphate
*p<0.05 vs. controls, by Mann-Whitney U-test

Gattorno M, *et al. Arthritis Rheum* 2008; **58**:1505–1515.

MRP8/14 induces IL-1β production

- **Peripheral blood mononuclear cells cultured in 20% serum from patients with active sJIA**



*Immunoprecipitation (IP) with anti-MRP8/14 antibody

Frosch M, *et al. Arthritis Rheum* 2009; **60**:883–891.

Inflammatory cytokines in sJIA

- **IL-1β[1]**
  - **Low or undetectable circulating levels**
  - **sJIA sera induce IL-1β production**
- **MRP8/14**
  - **Markedly elevated levels –diagnostic marker[2]**
  - **Correlation with disease activity[3]**
  - **Induces IL-1β production[4]**
- **IL-6[5–7]**

1. Pascual V, *et al. J Exp Med* 2005; **201**:1479–1486; 2. Frosch M, *et al. Arthritis Rheum* 2000; **43**:628–637; 3. Schulze zur Wiesch A, *et al. Clin Exp Rheumatol*. 2004; **22**:368–373; 4. Frosch M, *et al. Arthritis Rheum* 2009; **60**:883–891; 5. De Benedetti F, *et al. Arthritis Rheum* 1991; **34**:1158−1163; 6. De Benedetti F, *et al. Clin Exp Rheumatol* 1992; **10**:493−498; 7. De Benedetti F, *et al. J Rheumatol* 1997; **24**:1403−1409.

Inflammatory cytokines in sJIA

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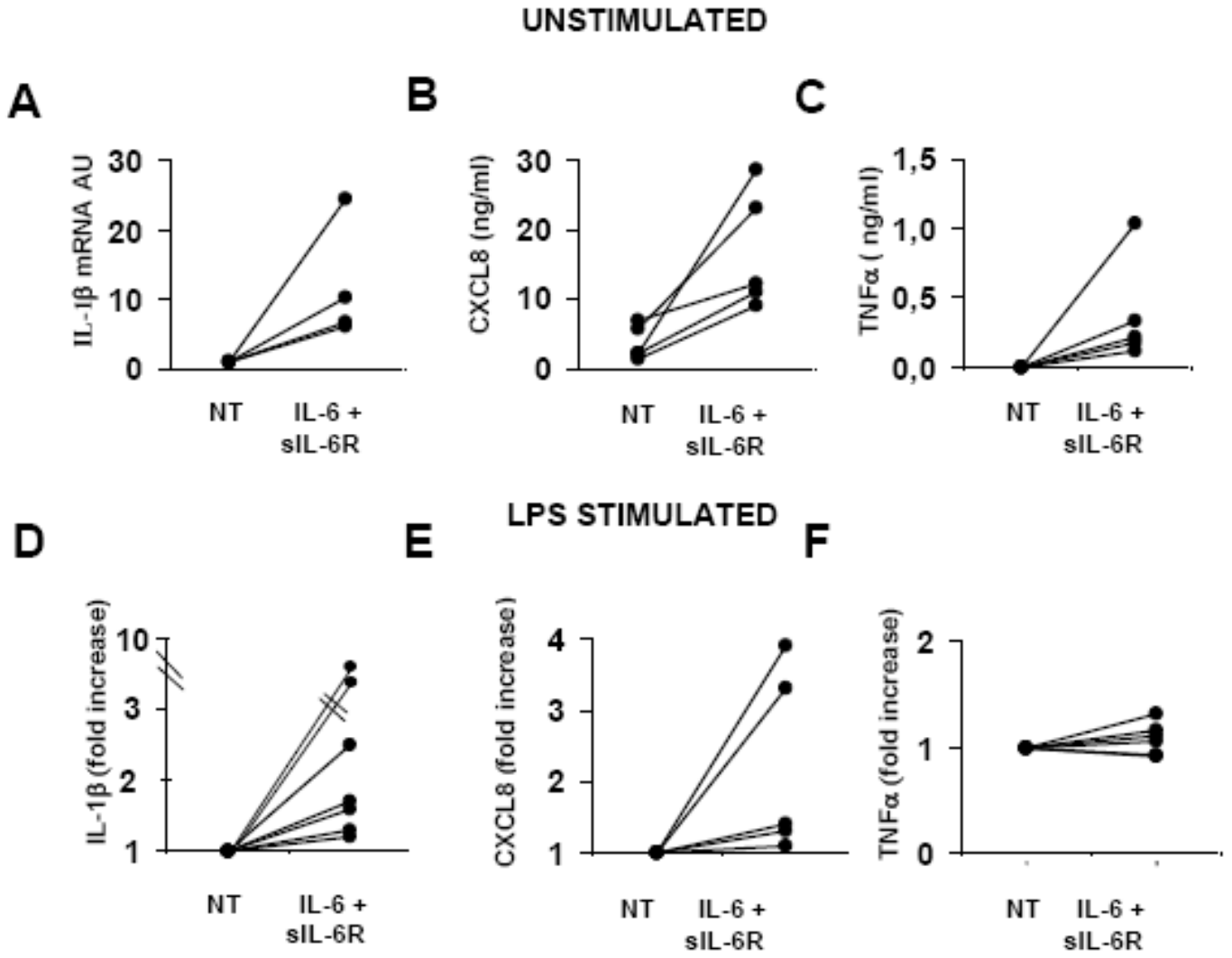
  - **Markedly elevated levels**
  - **Correlation with disease activity**

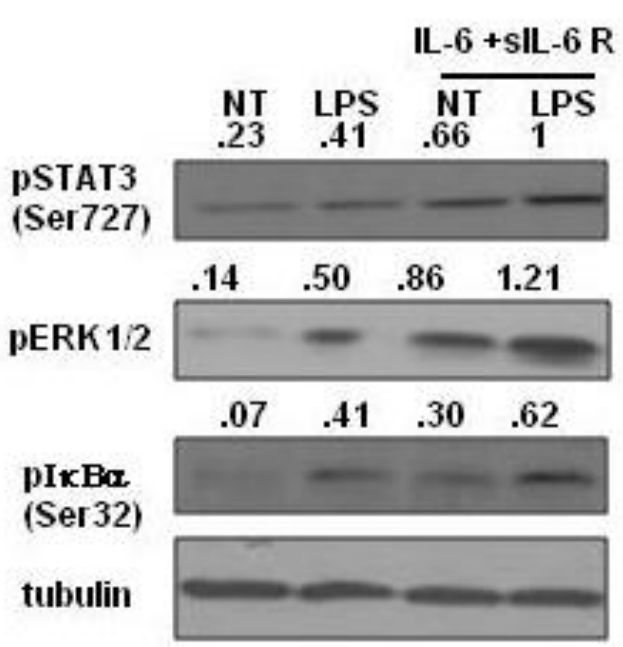
1. Pascual V, *et al. J Exp Med* 2005; **201**:1479–1486; 2. Frosch M, *et al. Arthritis Rheum* 2000; **43**:628–637; 3. Schulze zur Wiesch A, *et al. Clin Exp Rheumatol*. 2004; **22**:368–373; 4. Frosch M, *et al. Arthritis Rheum* 2009; **60**:883–891; 5. De Benedetti F, *et al. Arthritis Rheum* 1991; **34**:1158−1163; 6. De Benedetti F, *et al. Clin Exp Rheumatol* 1992; **10**:493−498; 7. De Benedetti F, *et al. J Rheumatol* 1997; **24**:1403−1409.

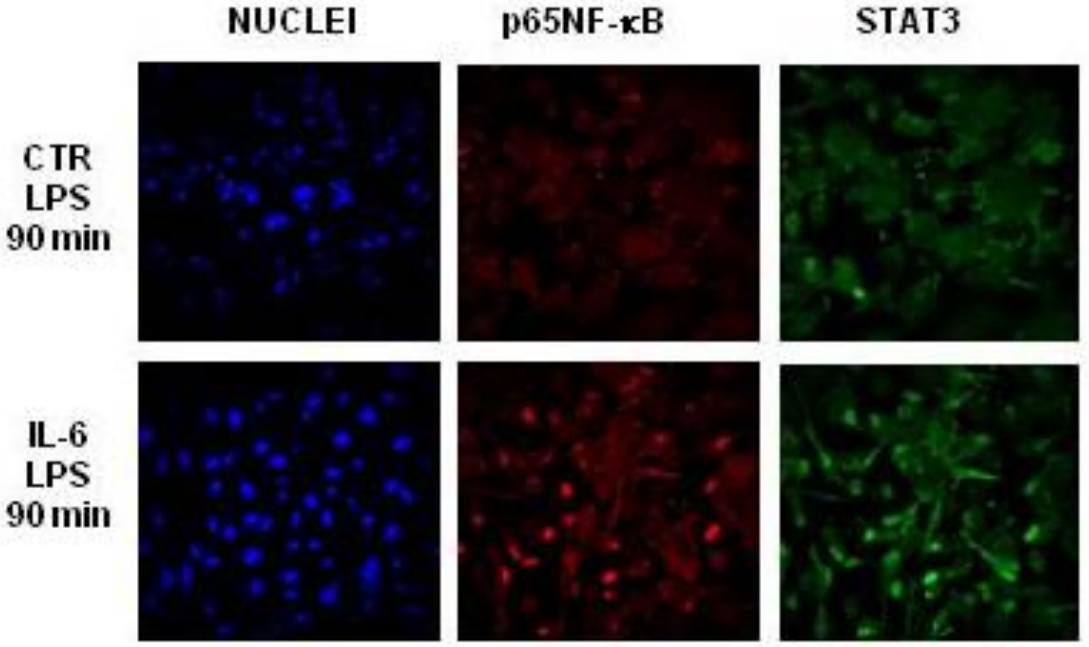
Preincubation with IL-6 induces IL-1β expression and production In vitro: evidence from human macrophages



IL-6 and cytokine responses

- **Preincubation with IL-6 + sIL-6R in human macrophages**

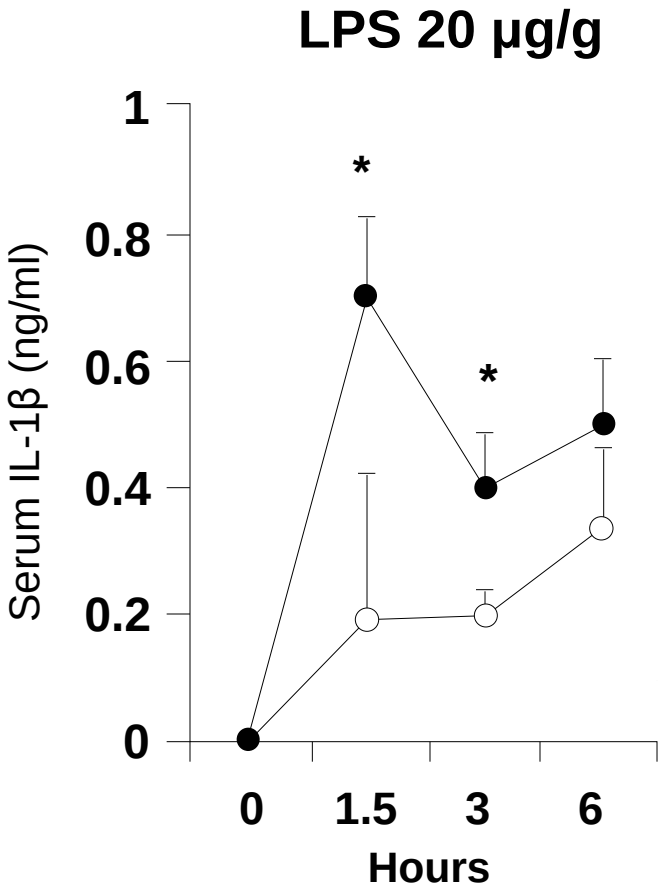


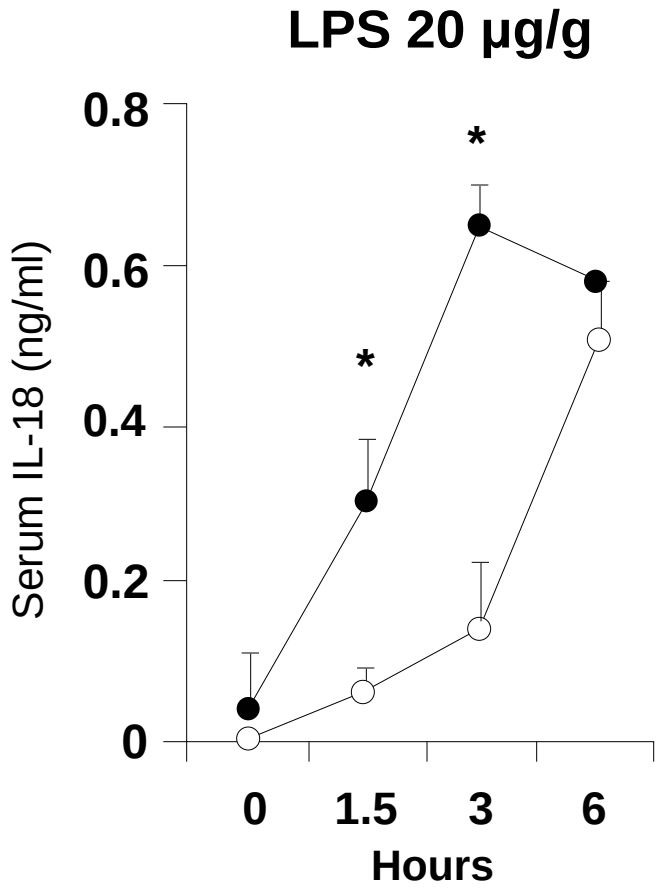


CTR = control

Strippoli R, *et al*. A&R in press

Exposure to high levels of IL-6 in vivo leads to increased IL-1β production in IL-6 transgenic mice





Strippoli R, *et al*. A&R in press

IL-6 induces IL-1 beta production

In vitro in human macrophages

- Increased IL-1 and chemokine production
- Increased NFκB nuclear translocation and MAP kinases activation following TLR activation

In vivo in IL-6 transgenic mice

- Increased production of IL-1β and il-18

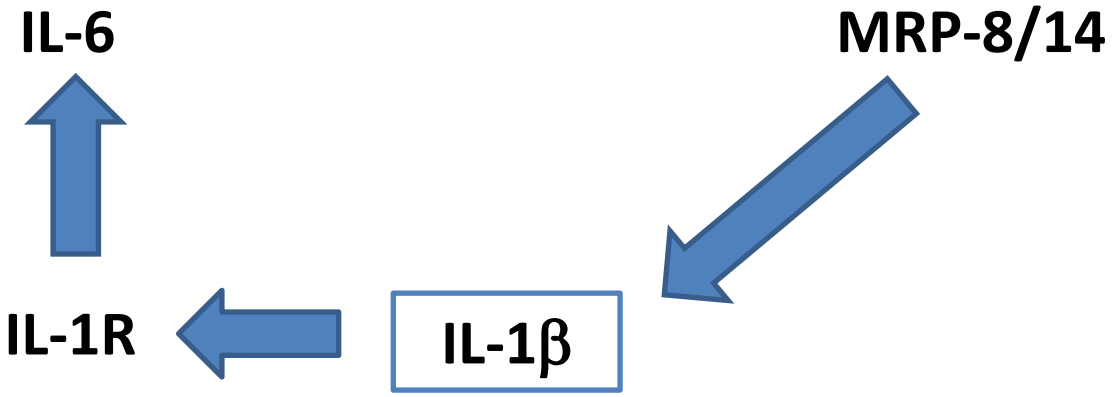
Inflammatory cytokine network in sJIA

- **IL-1β[1]**
  - **Low or undetectable circulating levels**
  - **sJIA sera induce IL-1β production**
- **MRP8/14**
  - **Markedly elevated levels[2]**
  - **Correlation with disease activity[3]**
  - **Induces IL-1β production[4]**
- **IL-6[5–7]**
  - **Markedly elevated levels**
  - **Correlation with disease activity**
  - **Induces IL-1β production**

1. Pascual V, *et al. J Exp Med* 2005; **201**:1479–1486; 2. Frosch M, *et al. Arthritis Rheum* 2000; **43**:628–637; 3. Schulze zur Wiesch A, *et al. Clin Exp Rheumatol*. 2004; **22**:368–373; 4. Frosch M, *et al. Arthritis Rheum* 2009; **60**:883–891; 5. De Benedetti F, *et al. Arthritis Rheum* 1991; **34**:1158−1163; 6. De Benedetti F, *et al. Clin Exp Rheumatol* 1992; **10**:493−498; 7. De Benedetti F, *et al. J Rheumatol* 1997; **24**:1403−1409.

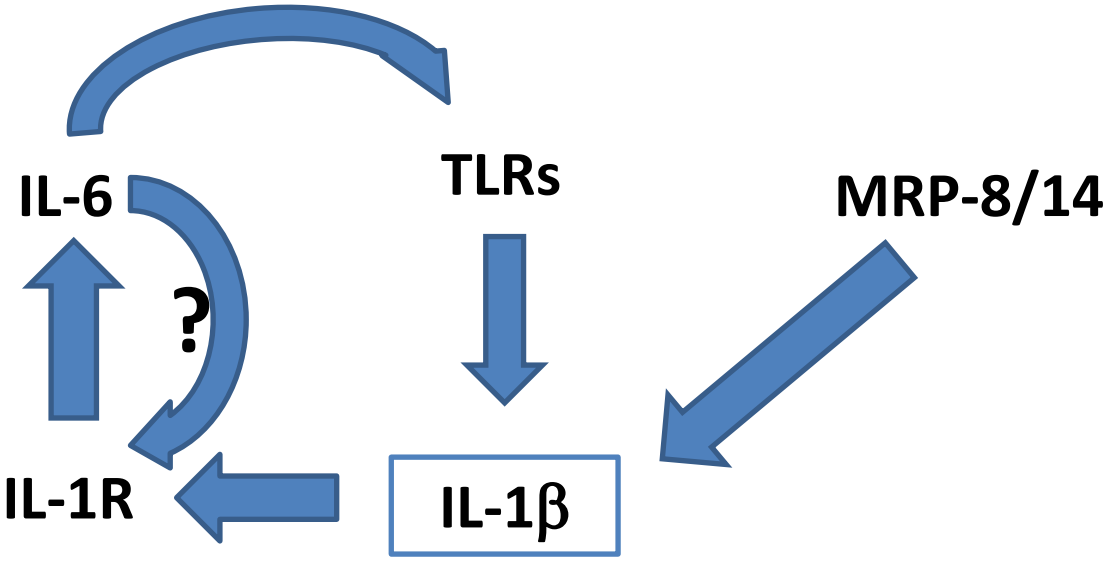
s-JIA: abnormal innate response

- response and circuits



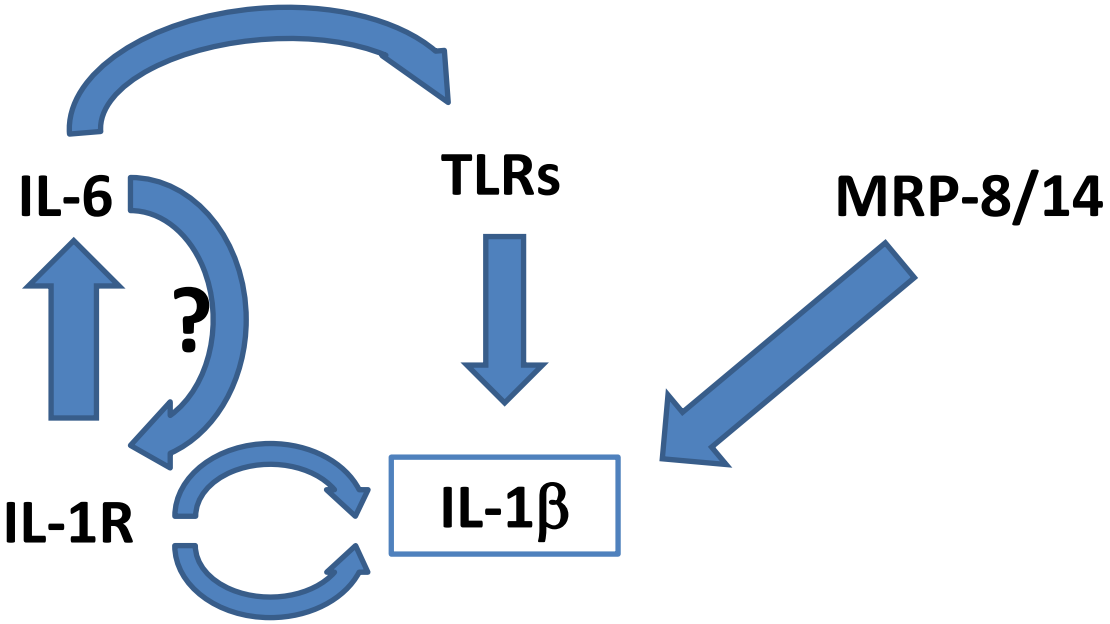
s-JIA: abnormal innate response

- response and circuits



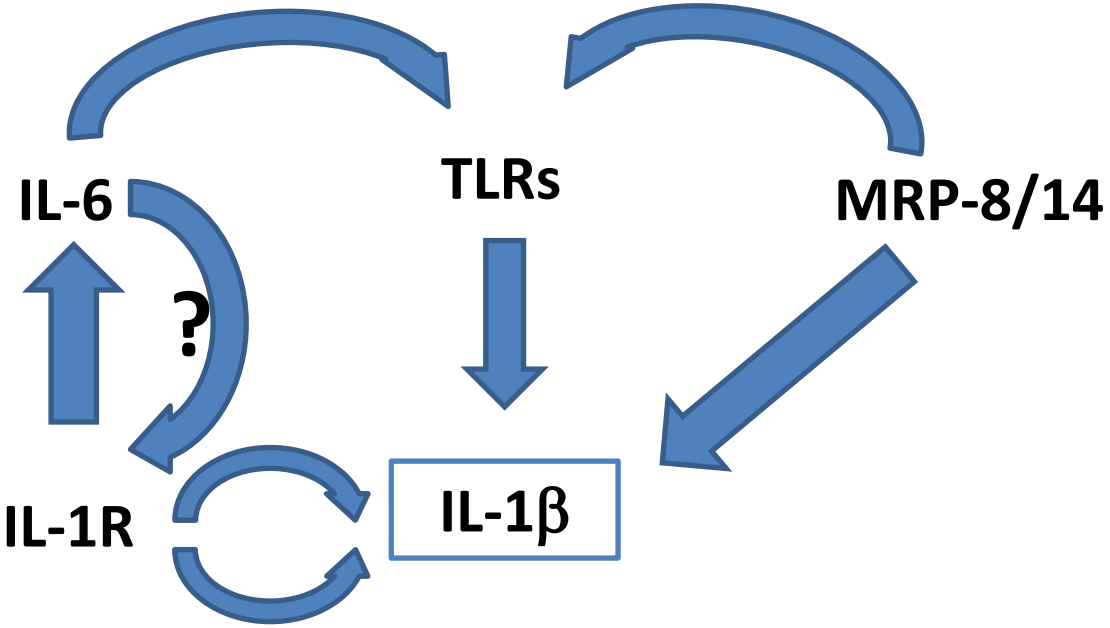
s-JIA: abnormal innate response

- response and circuits



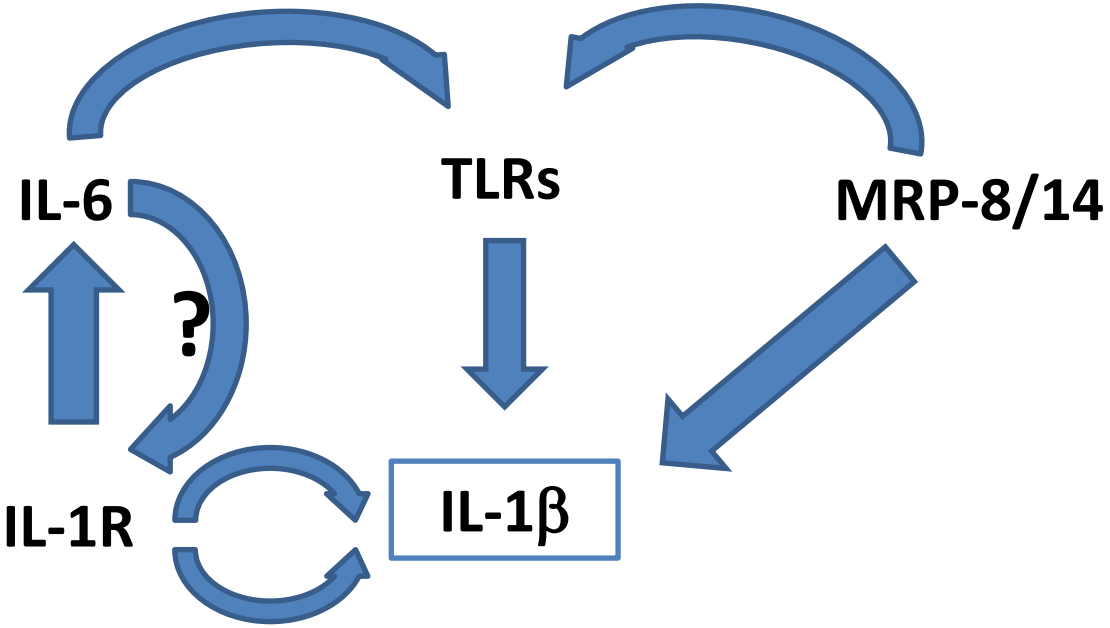
s-JIA: abnormal innate response

- response and circuits



s-JIA: abnormal innate response

- response and circuits



- defective regulation
  - IL-10
  - defective cytotoxic function

- **Role in systemic and local inflammatory responses**
  - **Unique biology of the soluble IL-6 receptor**
  - **Role in mononuclear cell recruitment**
- **IL-6 as target in s-JIA**
  - **The rational and the use of anti-IL-6 Tx as a probe for proof of concept**
- **Anti-IL-6 treatment in s-JIA**
  - **2 year data from TENDER with TCZ : efficacy, safety**
  - **1 year: PK; response according to baseline disease characteristics**
- **IL-1 and IL-6: in vitro and in vivo interplay**
  - **Up-stream or down stream? circuits**

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Felicity Schaefer

Stephen Wright

Andy Kenwright

Stuart Bolt

back-up slides

TENDER: Oral corticosteroid tapering

- **Allowed if ESR <20 mm/hr and**
  - **In double-blind phase at Weeks 6 and 8 (not at Week 10)**
    - **If absence of fever and JIA ACR70**
  - **In open-label extension phase (not at Weeks 24 and 50)**
    - **If absence of fever and JIA ACR50**
- **Not permitted more frequently than every 2 weeks**
- **Maximum tapering allowed: 20% of current (last visit) dose**

De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.
Roche: data on file.

TENDER: TCZ withdrawal in study Part III

- **Alternative TCZ dosing schedule permitted at Week 104 visit if for previous 12 consecutive weeks:**
  - **Inactive disease status**
  - **Oral corticosteroid-free**
  - **Stable MTX dose (if receiving)**
  - **Stable NSAIDs doses**
- **Occurs in 12-week steps only if inactive disease status is maintained**
- **Alternative TCZ schedule**
  - **TCZ every 3 weeks**
  - **TCZ every 4 weeks**
  - **No TCZ**
- **Patients must maintain inactive disease status to remain off TCZ**

Roche: data on file.

Japanese randomised withdrawal study in sJIA

Body weight and response

Patients NOT achieving	Completers Open Phase (n=50)	Body weight	
		BW <30 kg (n=29)	BW ≥30 kg (n=21)
JIA ACR30 and CRP <0.5mg/dl	6/50 (12%)	6/29 (21%)	0/21 (0%)
JIA ACR50	5/50 (10%)	5/29 (17%)	0/21 (0%)
JIA ACR70	14/50 (28%)	11/29 (37%)	3/21 (15%)

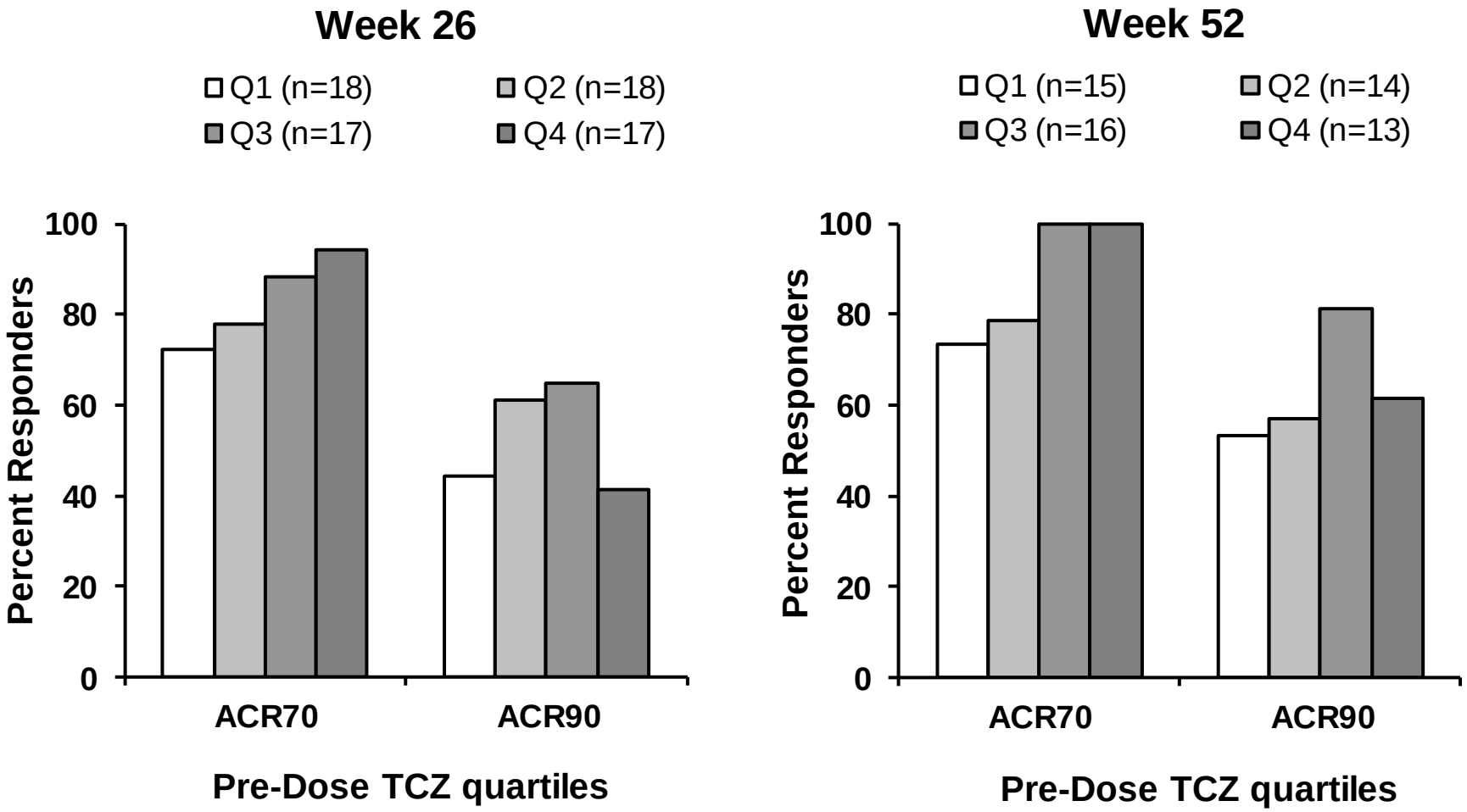
Yokota S, *et al. Lancet* 2008; **371**:998–1006.
Roche and Chugai: data on file.

TENDER: TCZ dosing regimen

- **Decreased efficacy associated with a trend for lower exposure to TCZ was observed in sJIA children with lower body weight**
- **Based on PK modeling of data from 56 children with sJIA**
- **TCZ administered i.v. every 2 weeks, dosed by baseline body weight**
  - **12 mg/kg for children body weight <30 kg every 2 weeks**
  - **8 mg/kg for children body weight ≥30 kg every 2 weeks**

Roche: data on file.

TENDER: JIA ACR70 and ACR90 responders by Pre-Dose TCZ serum concentration quartiles



Roche: data on file.

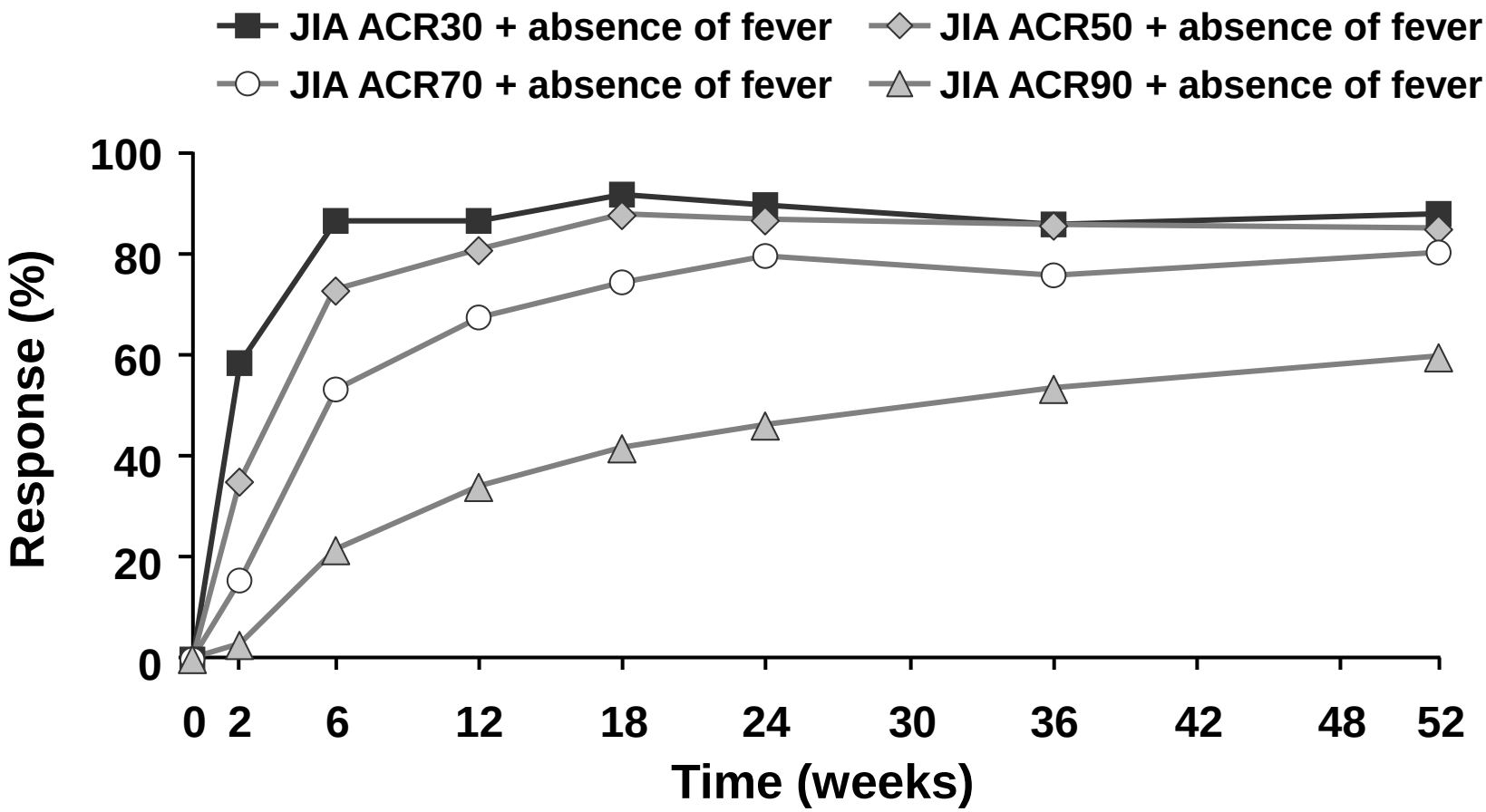
TENDER: Neutropenia at Week 52

- **Higher frequency of neutropenia compared to adults**
- **No association with infections**
- **No association with exposure**

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
C min (µg/ml) Week 52	N=26	N=2	N=16	N=14	N=0
	65.0±29.5	71.3±33.9	83.8±31.3	62.2±28.1	–

Roche: data on file.

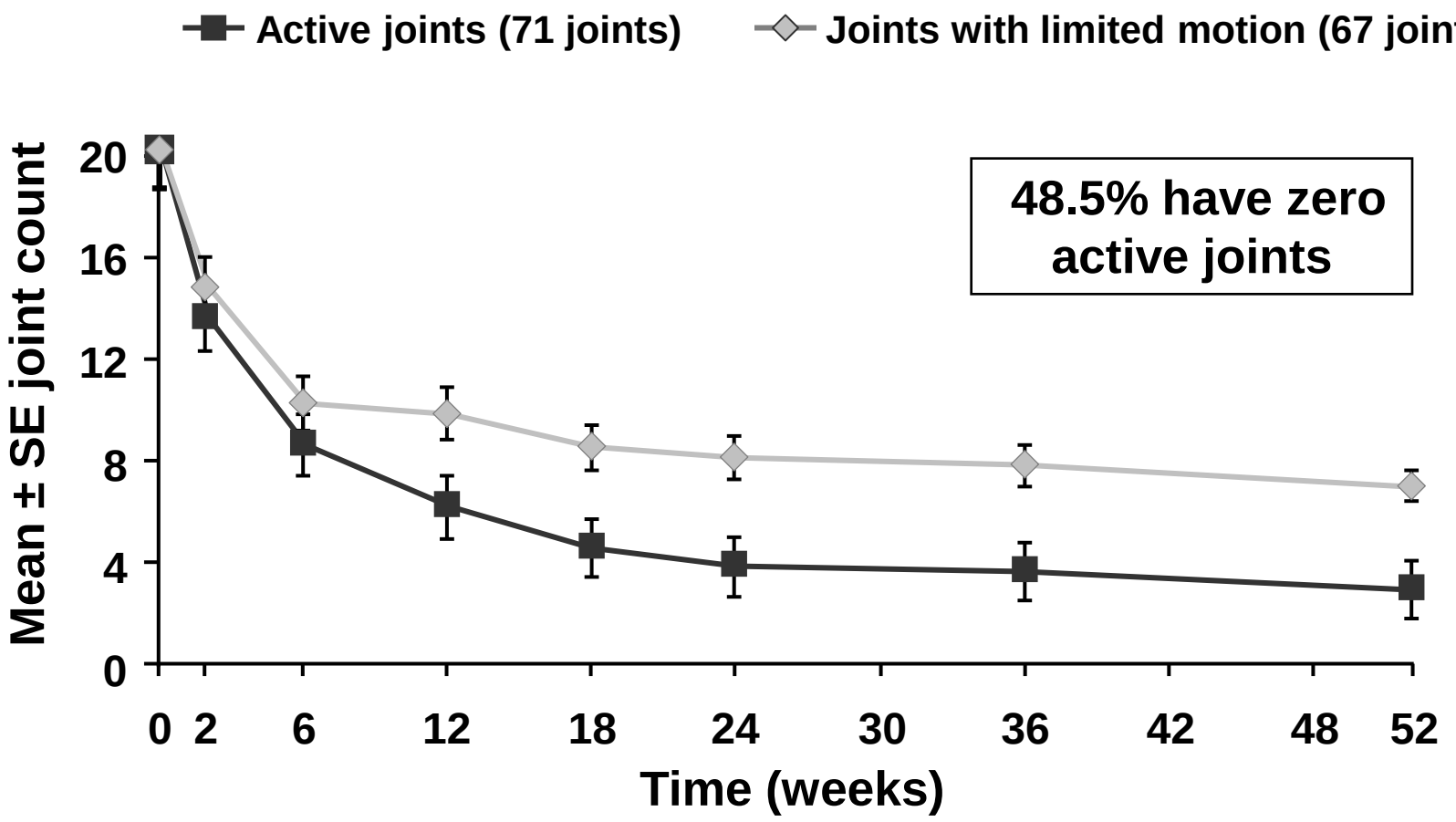
TENDER: JIA ACR responses + absence of fever over 52 weeks



*Three patients were not included in the Week 52 data because they had not yet reached that time point at the time of data cut. Patients who withdrew because of insufficient therapeutic response were classified as non-responders post-withdrawal. LOCF rule applied to missing JIA ACR core set components at visits. Baseline is the first dose of TCZ.

De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.

TENDER: Mean active joints and joints with limited motion over 52 weeks

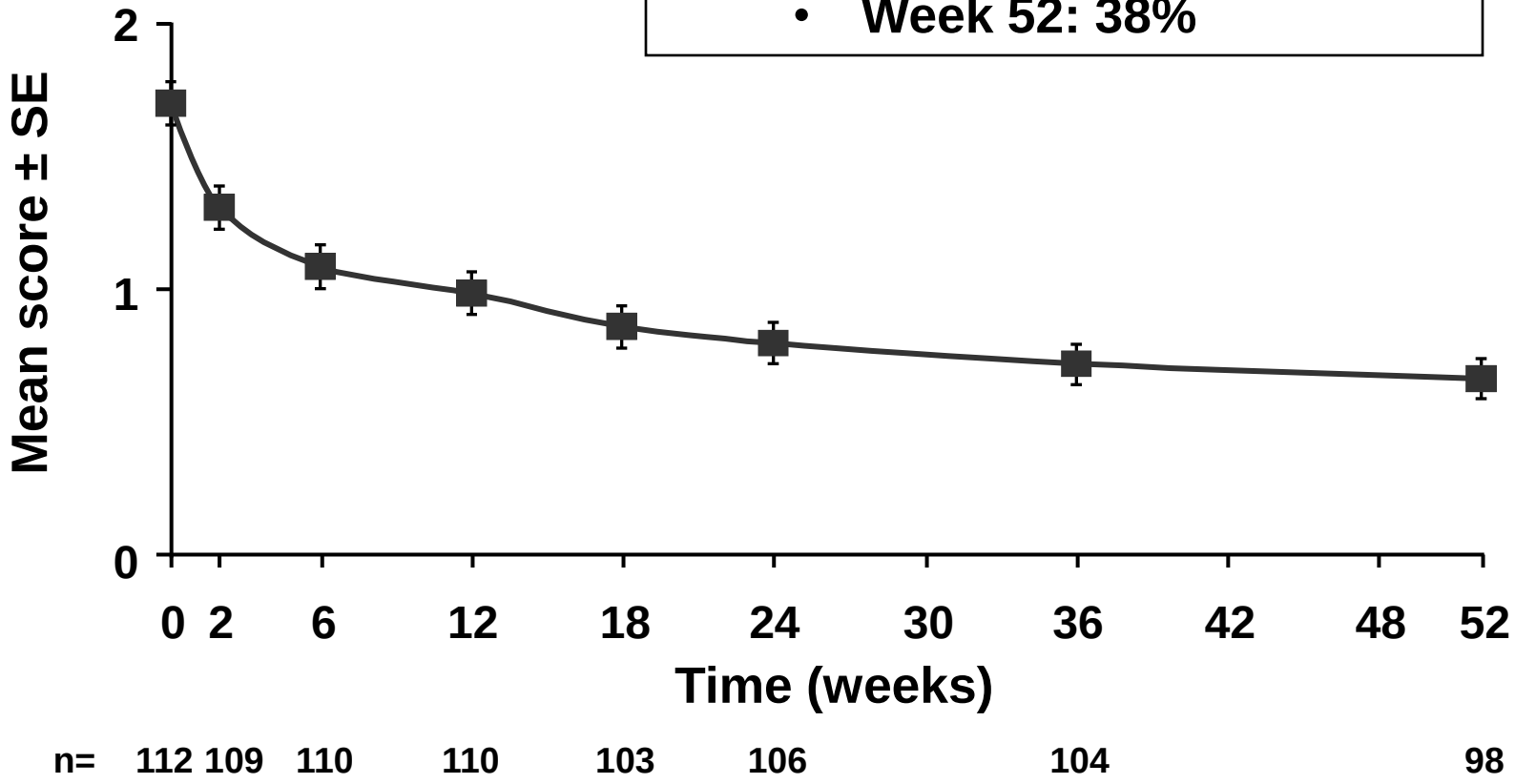


Three patients were not included in the Week 52 data because they had not yet reached that time point at the time of data cut. Baseline is the first dose of TCZ. “n” represents the number of patients with a non-missing assessment at the time point, and patients who previously withdrew are excluded.

De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.

TENDER: Mean CHAQ-DI over 52 weeks

% patients with CHAQ >0.75
- **Baseline: 82%**
- **Week 52: 38%**

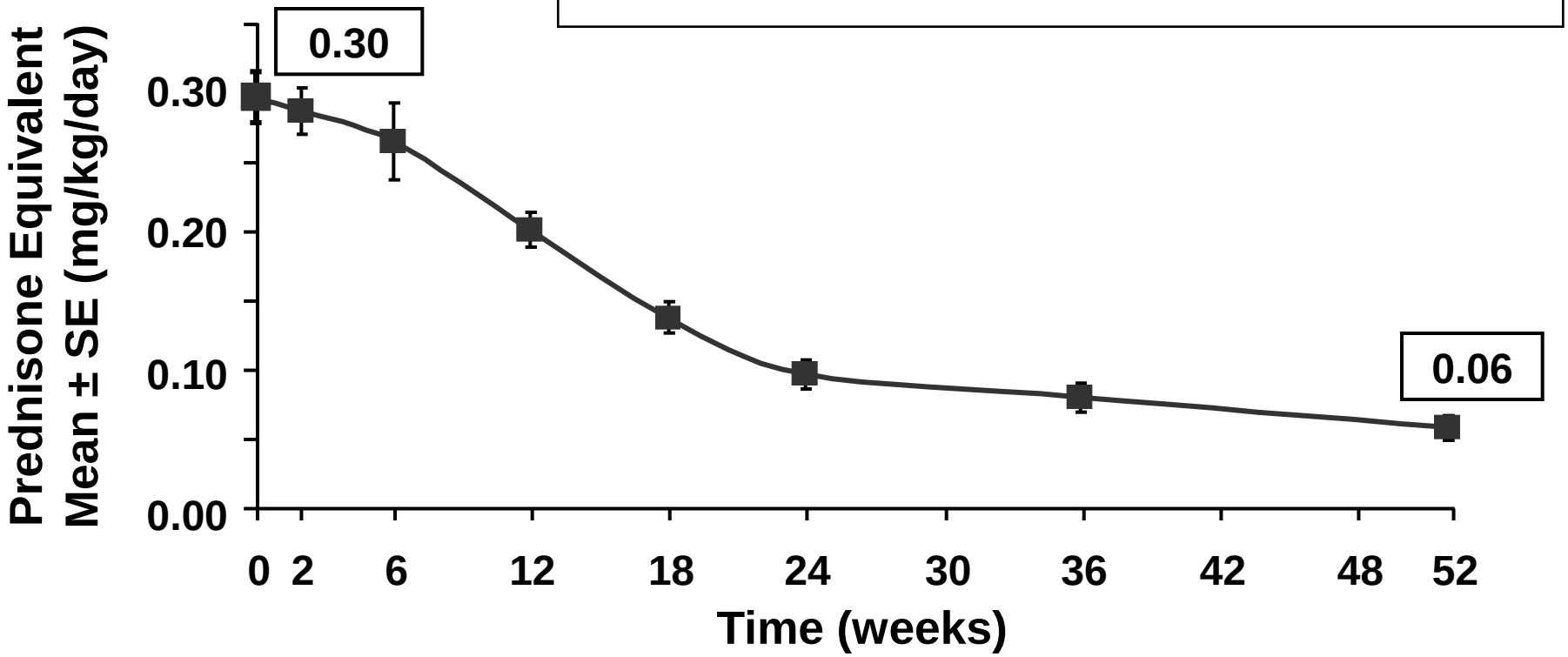


Three patients were not included in the Week 52 data because they had not yet reached that time point at the time of data cut. “n” represents the number of patients with a non-missing assessment at the time point, and patients who previously withdrew are excluded. Baseline is the first dose of TCZ.

Roche: data on file.

TENDER: Mean oral corticosteroid dose over 52 weeks

- **Mean dose decreased to 0.06 mg/kg/day**
- **52.5% are off corticosteroids at Week 52**



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De Benedetti F, *et al. Ann Rheum Dis* 2011; **70**(Suppl3):67.

Systemic Juvenile Idiopathic Arthritis

- **High dose corticosteroids highly effective**

- **Poor response to traditional DMARDs and to TNF inhibitors**

- Some patients show favorable response to IL-1 inhibitors

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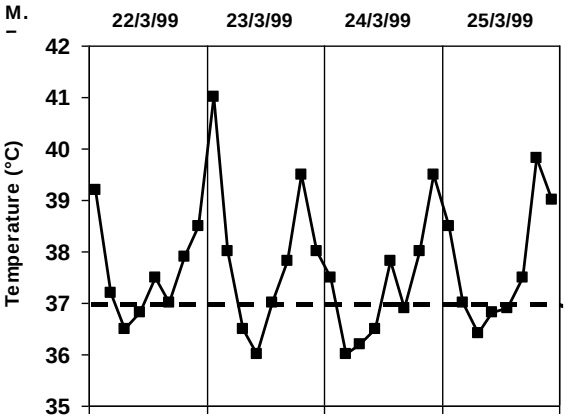
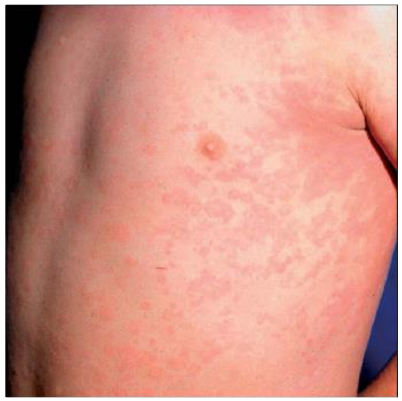
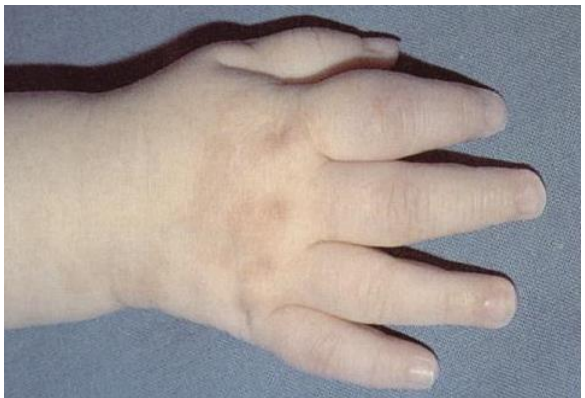


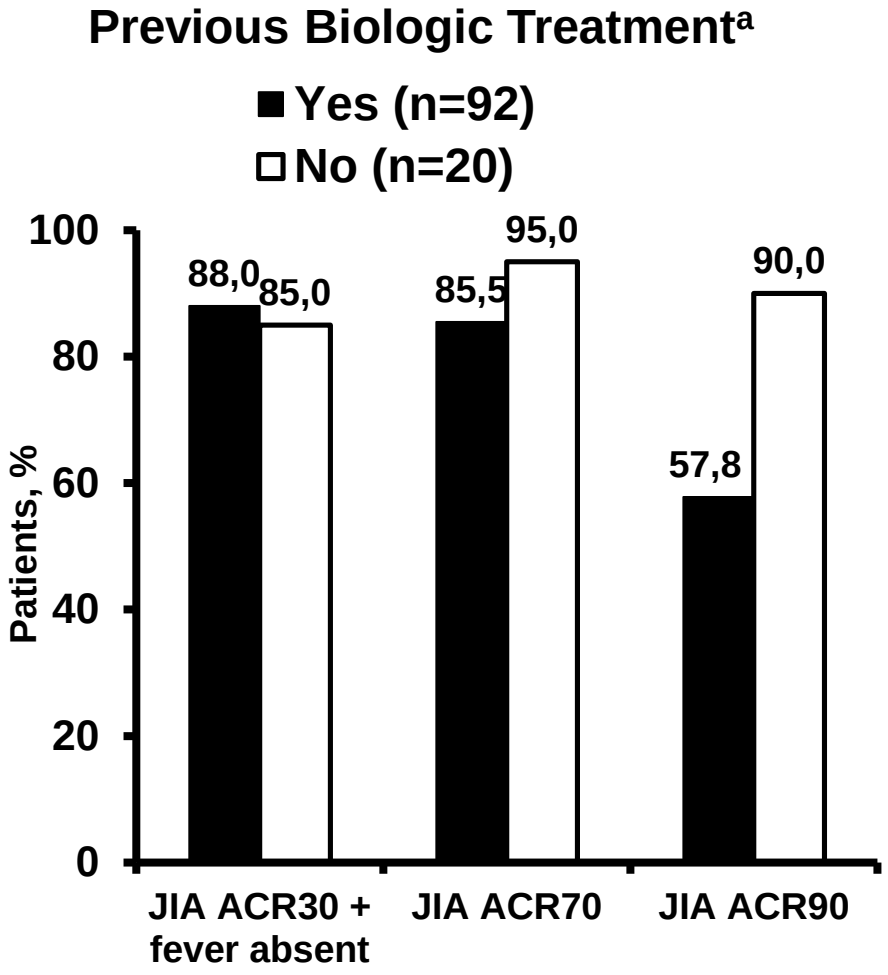


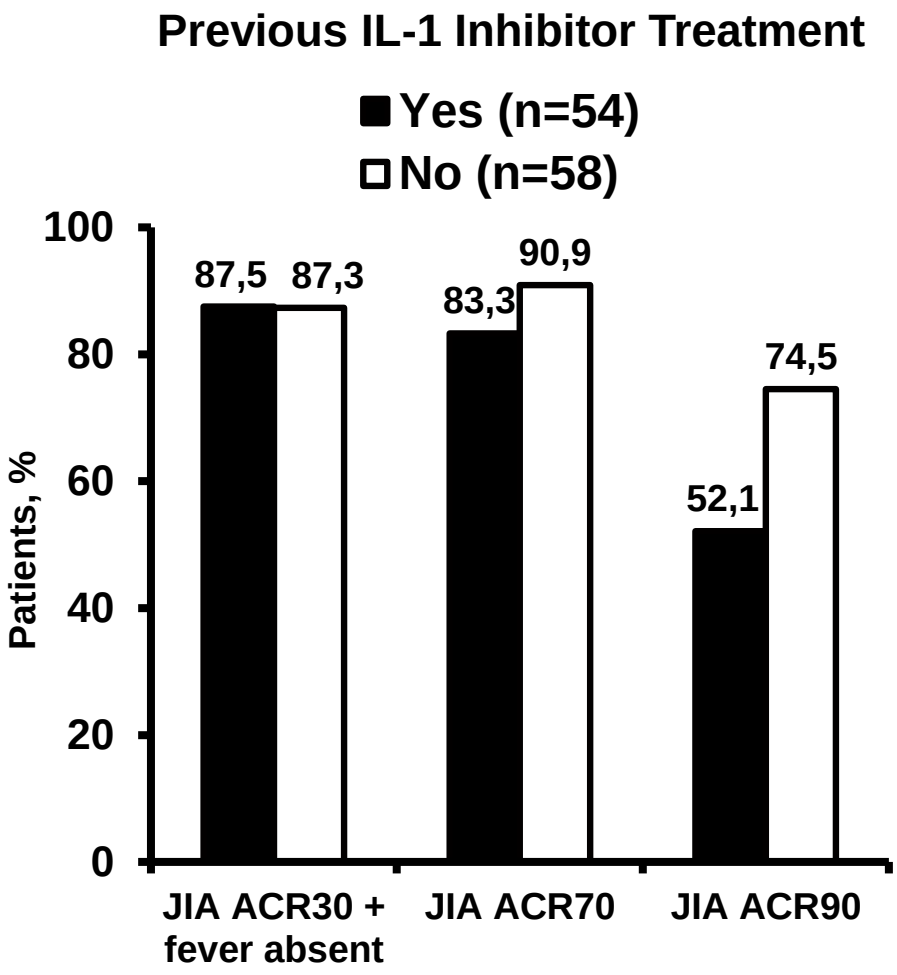


Infections

	N = 112
Infections and infestations/100 PY	282.1 (570)
Serious infection AEs/100 PY (n)	10.9 (22)
Infections (remotely, possibly, probably) related to study treatment	8
Gastroenteritis	1
Otitis media	1
Pharyngotonsillitis	1
Septic arthritis	1
Streptococcal sepsis	1
Tonsillitis	1
Upper respiratory infection	1
Varicella	1

Response by Previous Biologic Treatment and Previous IL-1 Inhibitor Treatment



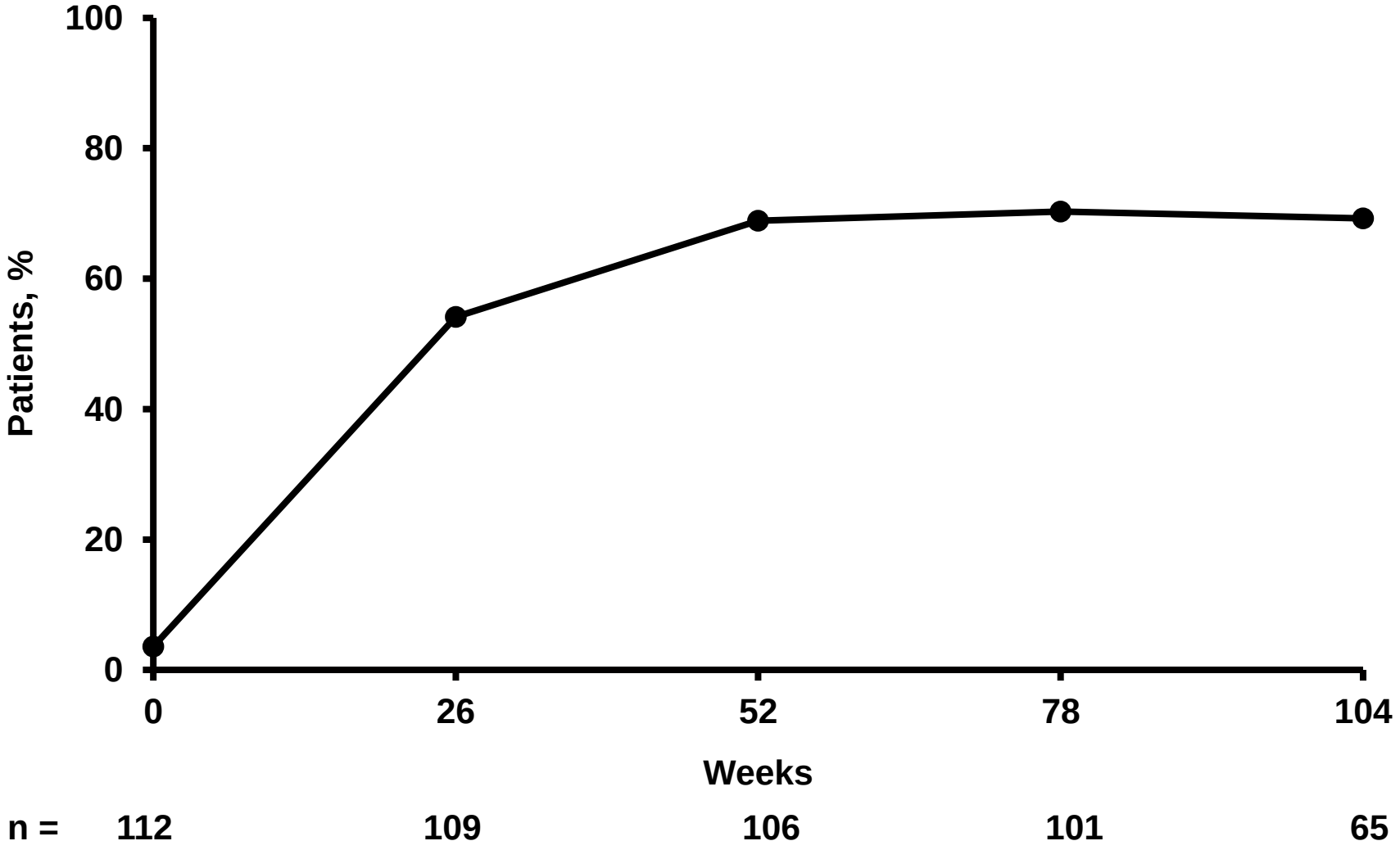


[a]TNF inhibitors, n=8; T cell co-stimulation inhibitors, n=7; IL-1 inhibitor, n=54; vaccines, toxoids and serologic agents, n=22; cytokines, n=1

TENDER: Oral Corticosteroid Tapering

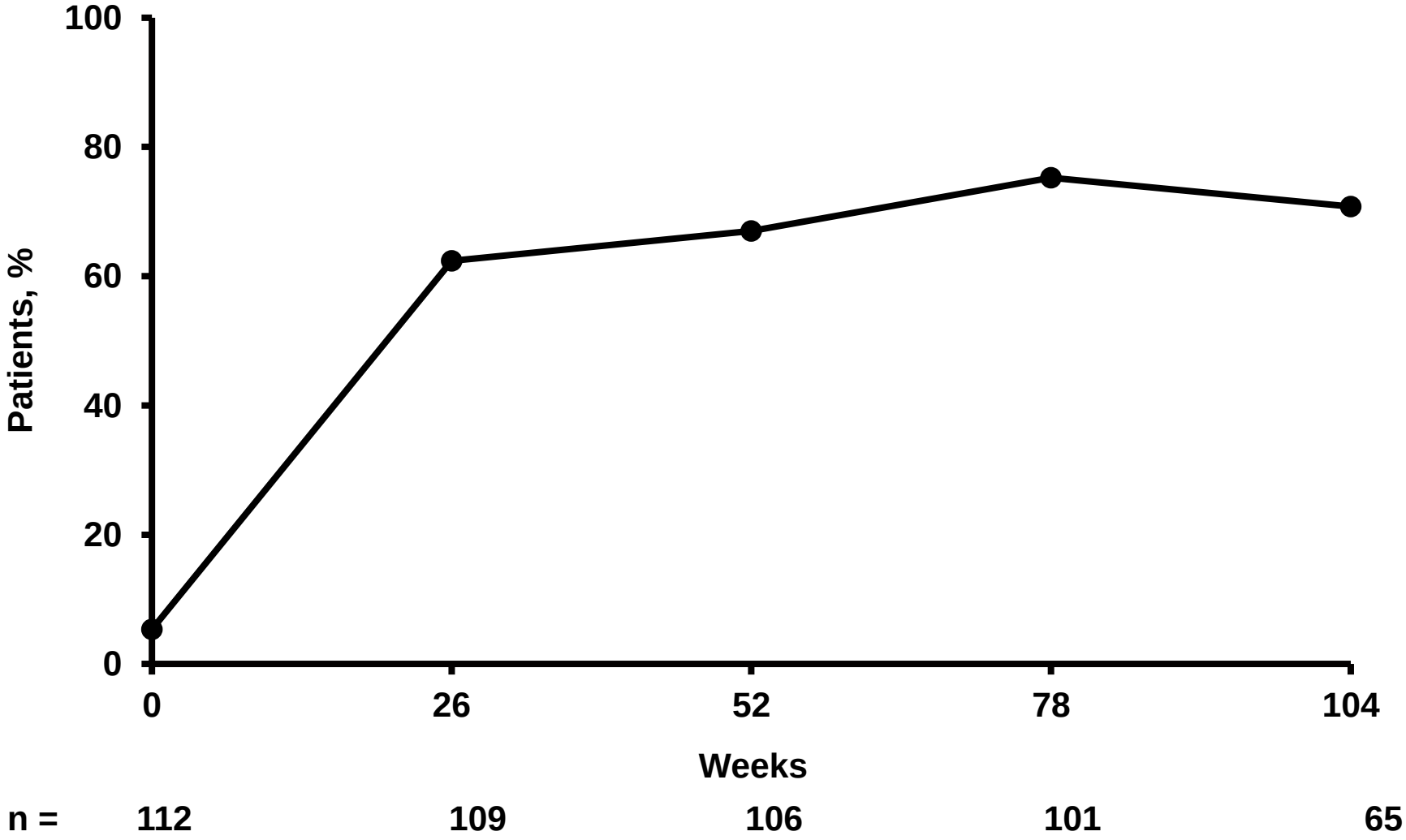
- Allowed if ESR <20 mm/hr and
  - In double-blind phase at weeks 6 and 8 (not at week 10)
    - If absence of fever and JIA ACR70
  - In open-label extension phase (not at weeks 24, 50, 76, and 102)
    - If absence of fever and JIA ACR50
- Not permitted more frequently than every 2 weeks
- Maximum tapering allowed: 20% of current (last visit) dose in double-blind phase and at investigator's discretion in open-label

Physician Global Assessment VAS ≤10 mm

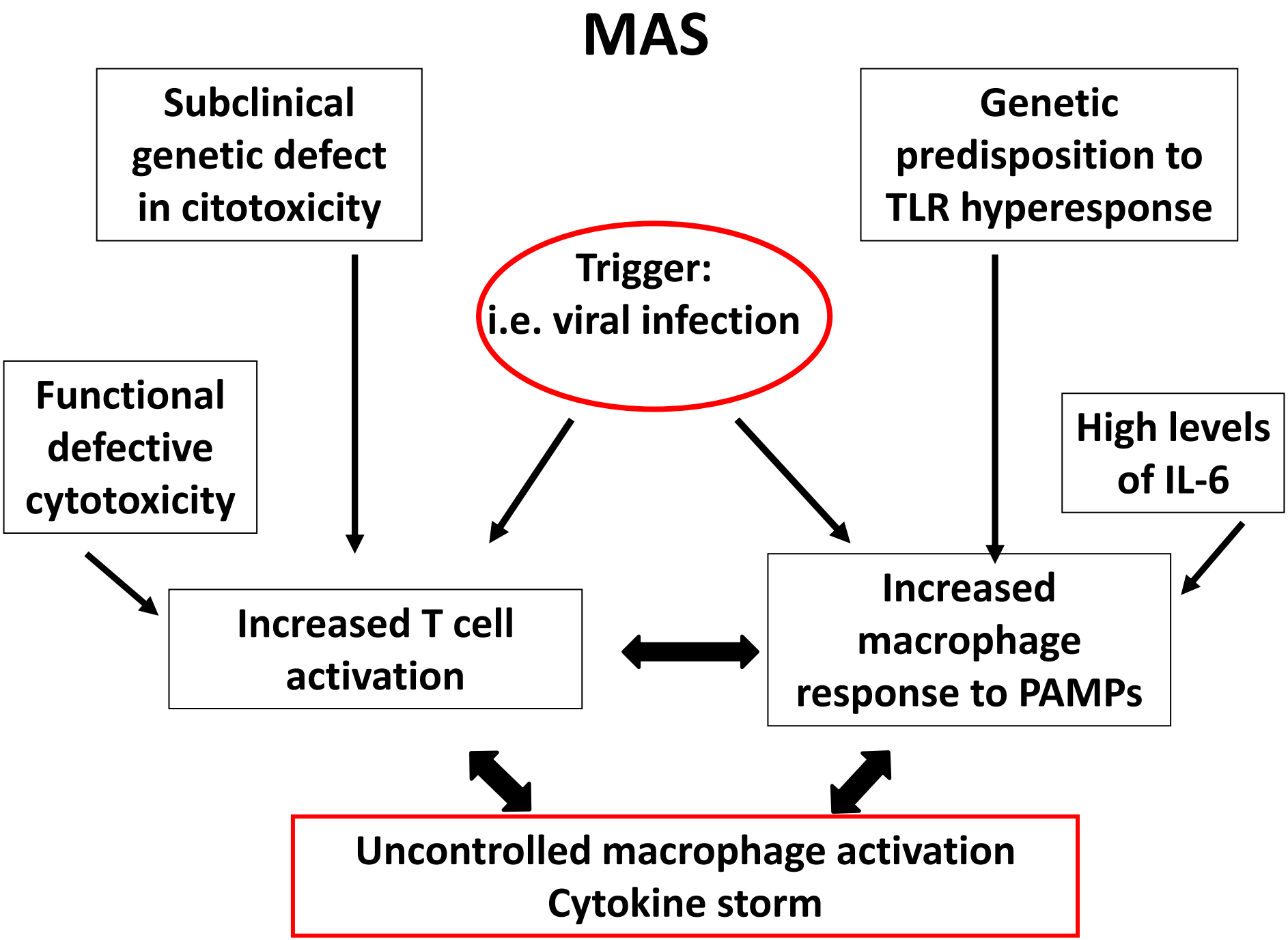


Percentage is based on number of pts who reached time point + pts who withdrew because of insufficient therapeutic response and are assumed to have been nonresponders.

Patient/Parent Global Assessment VAS ≤10 mm



Percentage is based on number of pts who reached time point + pts who withdrew because of insufficient therapeutic response and are assumed to have been nonresponders.


MAS
Subclinical genetic defect in citotoxicity
Genetic predisposition to TLR hyperesponse
Trigger: i.e. viral infection
Functional defective cytotoxicity
High levels of IL-6
Increased T cell activation
Increased macrophage response to PAMPs
Uncontrolled macrophage activation
Cytokine storm