Systemic juvenile idiopathic arthritis

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Juvenile idiopathic arthritis: diagnostic criteria

- Any arthritis:
  - lasting for more than 6 weeks
  - of unknown origin
  - with onset before 16 years of age

	Frequency*	Onset age	Sex ratio
Systemic arthritis	4–17%	Throughout childhood	F=M
Oligoarthritis	27–56%	Early childhood; peak at 2–4 years	F>>>M
Rheumatoid-factor-positive polyarthritis	2–7%	Late childhood or adolescence	F>>M
Rheumatoid-factor-negative polyarthritis	11–28%	Biphasic distribution; early peak at 2–4 years and later peak at 6–12 years	F>>M
Enthesitis-related arthritis	3–11%	Late childhood or adolescence	M>>F
Psoriatic arthritis	2–11%	Biphasic distribution; early peak at 2–4 years and later peak at 9–11 years	F>M
Undifferentiated arthritis	11–21%	..	..

*Reported frequencies refer to percentage of all juvenile idiopathic arthritis.

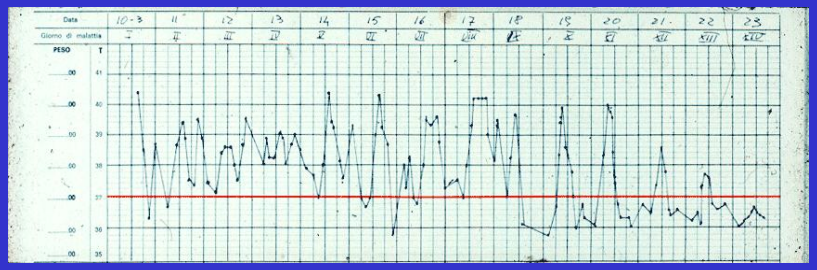
Table 1: **Frequency, age at onset, and sex distribution of the International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis**

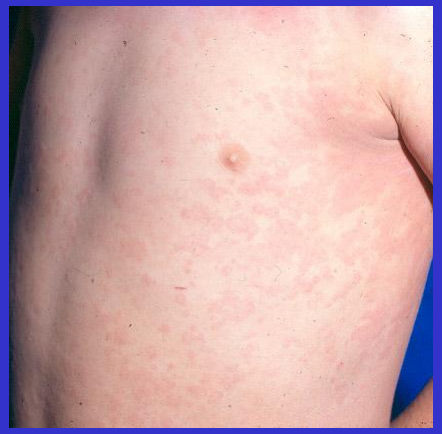
Juvenile idiopathic arthritis

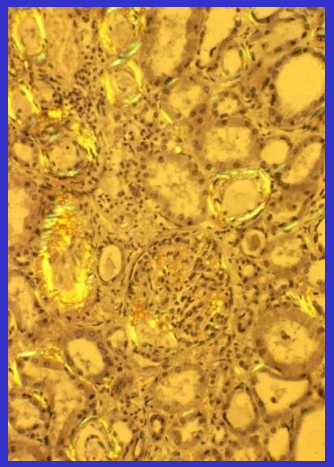
Angelo Ravelli, Alberto Martini

Lancet 2007; 369: 767–78

Systemic JIA







Serositis

Hepatosplenomegaly

Lymphodenopathy

Arthritis

ESR and CRP +++

Neutrophilic leukocytosis

Thrombocytosis +++

Ferritin +++

Microcytic anemia

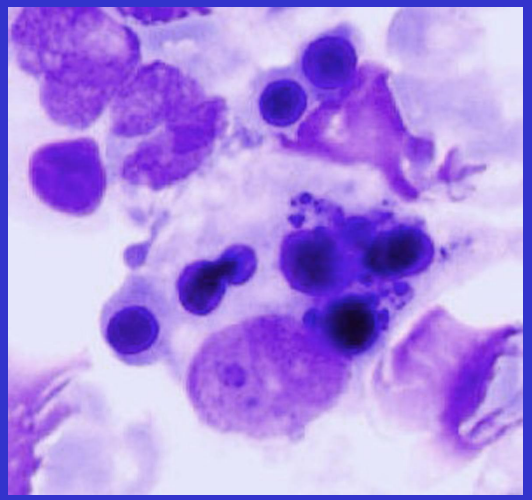
ANA and RF negative

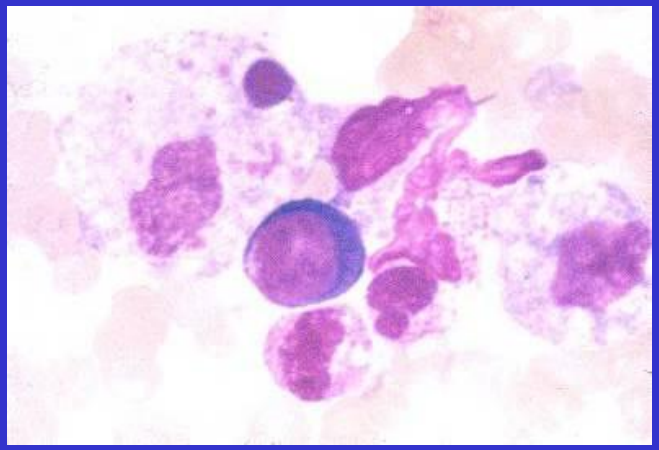
Systemic JIA

- Equal sex incidence, may occur at any age
- Rare in adults (adult-onset Still's disease)
- Heterogeneous outcome:
  - ~ 50% systemic flares with little persistent arthritis
  - ~ 50% chronic, severe arthritis with or without persistence of systemic symptoms
- ~ 30% severe joint damage

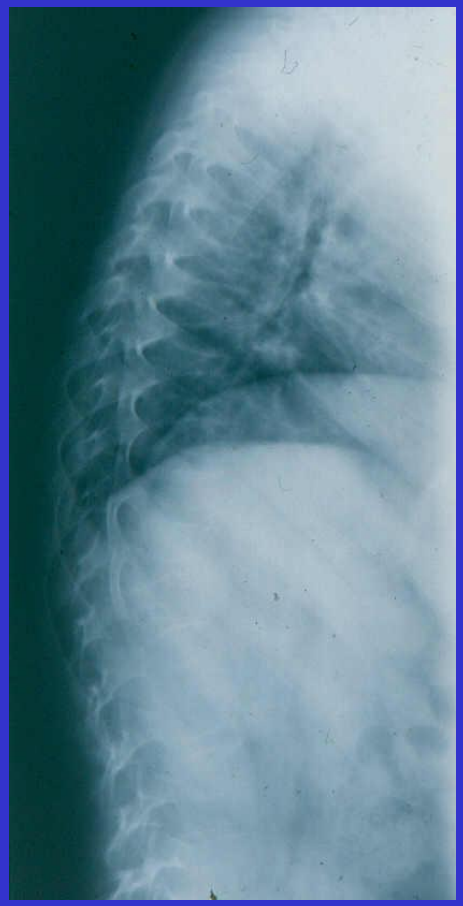
Macrophage activation syndrome (reactive hemophagocytic lymphohistiocytosis)

- ~ 10% of patients
- Fever (continuous)
- ↑Acute liver enlargement
- ↑ AST, ALT, CK
- ferritin
- Cytopenia with marked neutropenia
- ↑ triglycerides
- Coagulopathy
- CNS dysfunction





Treatment



NSAIDs

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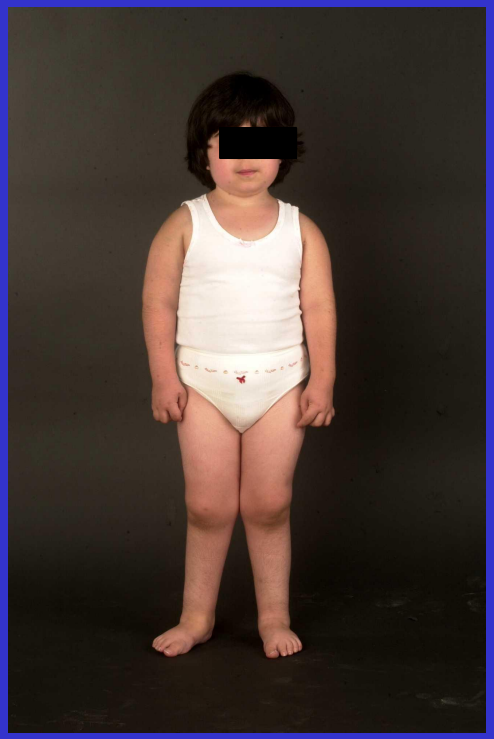
Steroids

± MTX



Anti-TNF in systemic JIA

- Children with sJIA do not respond as well to anti-TNF agents as those with other forms of JIA

Quartier et al Arthritis Rheum 2003 48:1093

Kimura et al J Rheumatol 2005;32.935

IL-6 and systemic JIA

Arthritis Rheum 1991;34:1158-63; *J Clin Invest* 1994;93:2114-9; *Lancet* 1994;344:1052-4; *Blood* 1996;87:4824-30; *J Clin Invest* 1997;99:643-50

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De Benedetti F., Martini A.: Is systemic juvenile rheumatoid arthritis an interleukin-6 mediated disease? J *Rheumatol* 25; 203-7, 1998

↓

Yokota S et al : Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet.* 2008;371:998-1006

Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial

Shumpei Yokota, Tomoyuki Imagawa, Masaaki Mori, Takako Miyamae, Yukoh Aihara, Shuji Takei, Naomi Iwata, Hiroaki Umebayashi, Takuji Murata, Mari Miyoshi, Minako Tomiita, Norihiro Nishimoto, Tadamitsu Kishimoto

Lancet 2008; 371: 998–1006

6 weeks open label lead-in phase

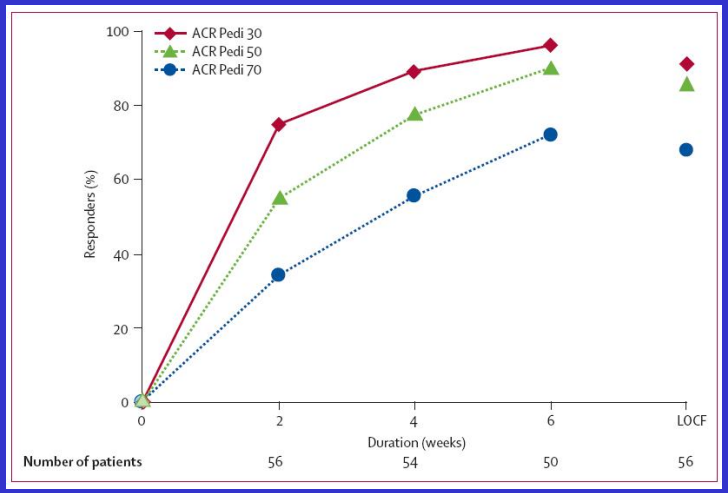
12 weeks randomized placebo-controlled phase

56 pts, 8mg/kg tocilizumab (anti-IL-6R moAb) every other week

Inclusion criteria: CRP ≥15 mg/L and inadequate response to corticosteroids (at ≥0.2 mg/kg prednisolone equivalent)

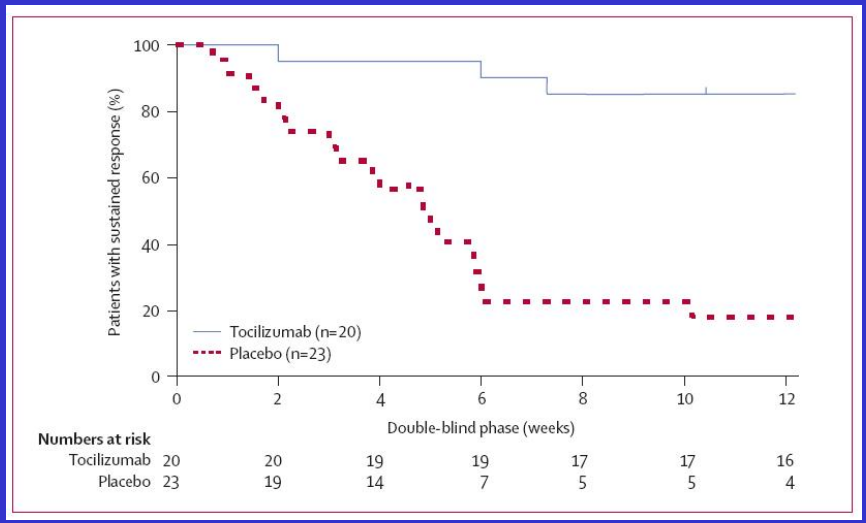
Response: ACR Pedi 30 + CRP < 5mg/L

ACR Pedi 30 + CRP
< 5mg/L



43/56 patients entered the double-blind phase

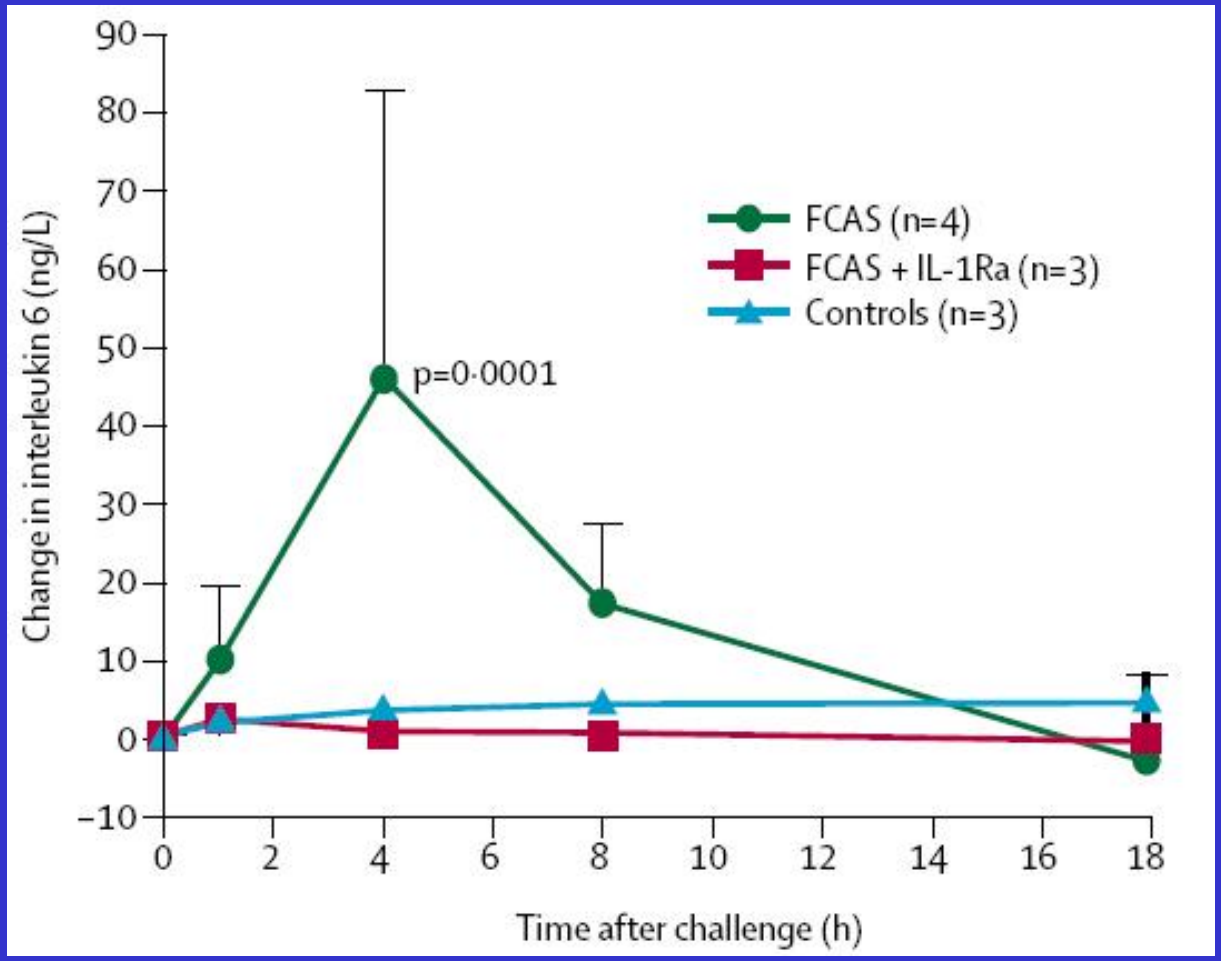
Maintain ACR Pedi 30 response and CRP <15mg/L



Yokota et al Lancet 2008;371:998

Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist

Hal M Hoffman, Sanna Rosengren, David L Boyle, Jae Y Cho, Jyothi Nayar, James L Mueller, Justin P Anderson, Alan A Wanderer, Gary S Firestein

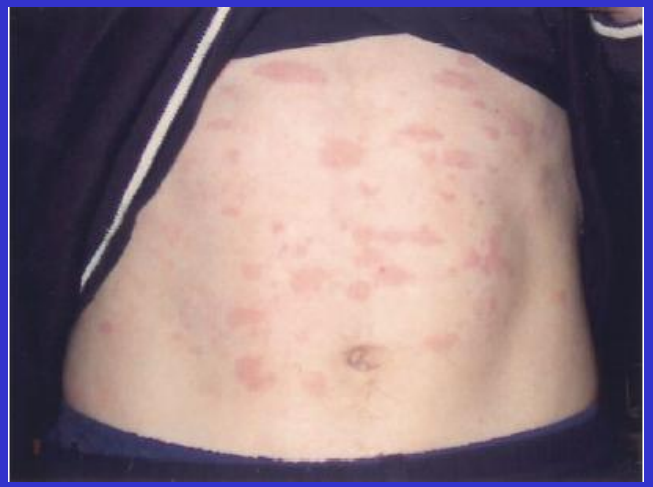


ARTHRITIS & RHEUMATISM
Vol. 50, No. 2, February 2004, pp 607–612
DOI 10.1002/art.20033

Spectrum of Clinical Features in Muckle-Wells Syndrome and Response to Anakinra

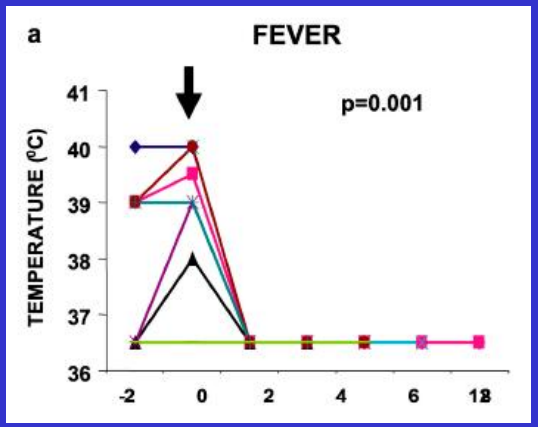
Philip N. Hawkins,[1] Helen J. Lachmann,[1] Ebun Aganna,[2] and Michael F. McDermott[2]

Patient, parameter	Baseline	Anakinra treatment		
		1 week	4 weeks	12 weeks
Mother				
Serum amyloid A, mg/liter	146	<1.0	<1.0	1.3
C-reactive protein, mg/liter	56	2.2	1.1	1.3
Hemoglobin, gm/dl	11.5		12.3	14.4
Leukocyte count, 10^9/liter	13.8		8.5	9.9
Platelet count, 10^9/liter	312		154	198
Son				
Serum amyloid A, mg/liter	264	2.8	2.3	2.2
C-reactive protein, mg/liter	129	4.1	4.3	4.3
Hemoglobin, gm/dl	12.1		13.3	14.1
Leukocyte count, 10^9/liter	13.2		6.2	5.9
Platelet count, 10^9/liter	421		231	246
Daughter				
Serum amyloid A, mg/liter	193	2.9	1.9	1.8
C-reactive protein, mg/liter	59	1.7	0.9	0.9
Hemoglobin, gm/dl	7.3		9.4	11.5
Leukocyte count, 10^9/liter	14.5		10.5	9.8
Platelet count, 10^9/liter	659		327	331

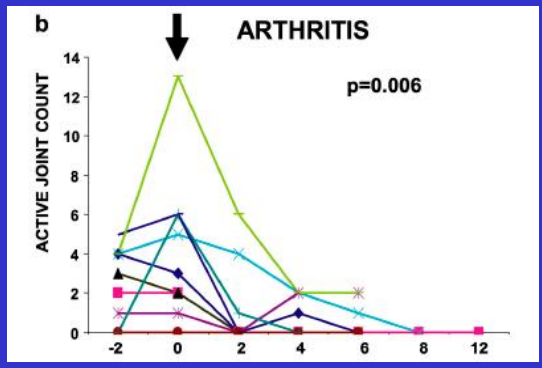


Pascual et al: Role of IL-1 in the pathogenesis of sJIA and clinical response to IL-1 blockade. *J Exp Med 2005;201:1479-86*

- Treatment with Anakinra was associated with complete remission in 7/9 patients and partial response in the other 2



- Upon activation, sJIA PBMCs release large amounts of IL-1β



Anakinra in sJIA and adult-onset Still's disease

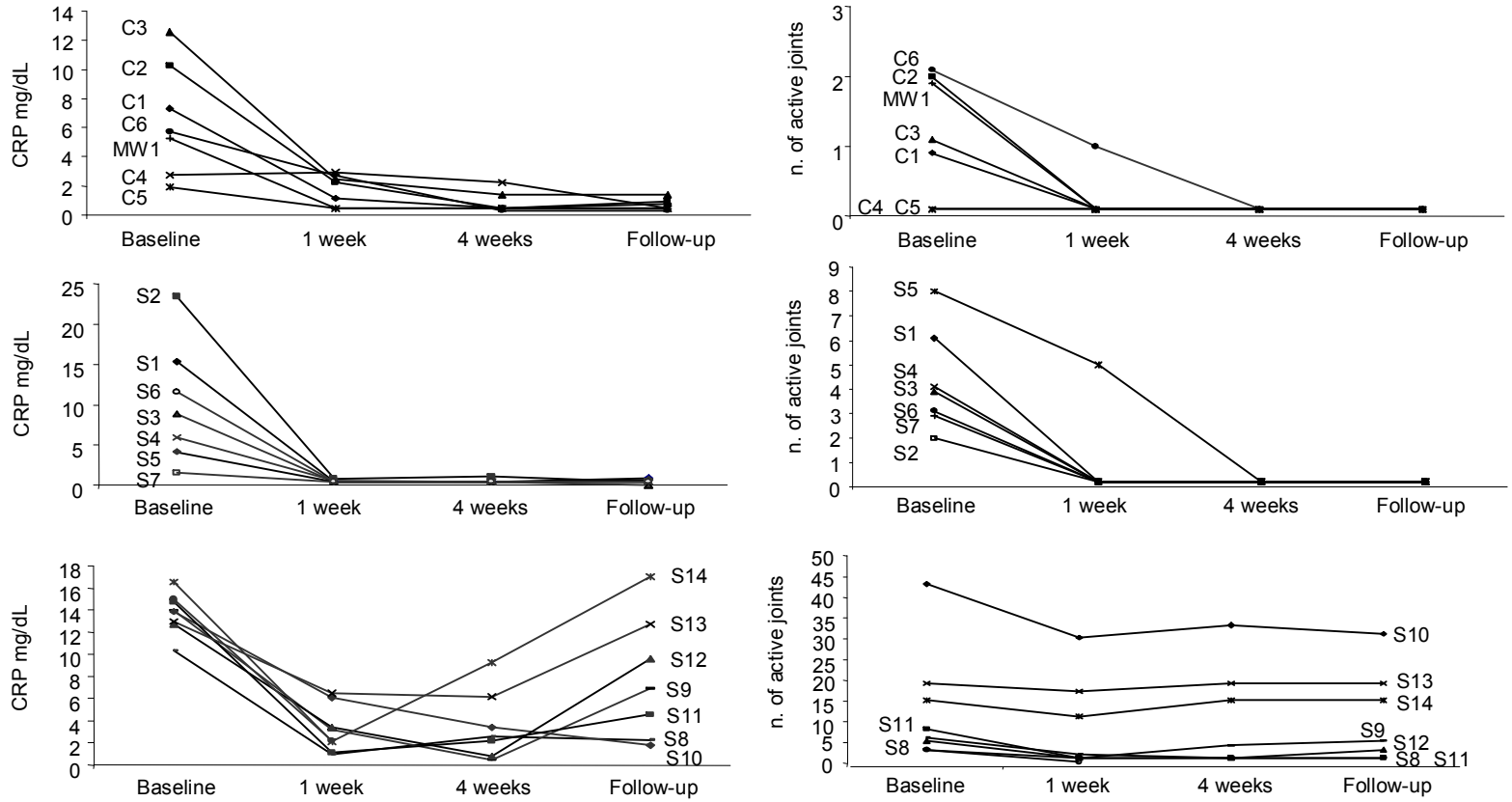
- Rapid response in 2 patients with sJIA *Verbsky et al J Rheumatol 2004;31:2071*
- Rapid response in 4 patients with AoSD *Fitzgerald et al Arthritis Rheum 2005;52:1794*
- 50% response in 5/20 sJIA and 11/15 AoSD *Lequerré T et al Ann Rheum Dis 2008;67:302*

CINCA

Syst

A

B

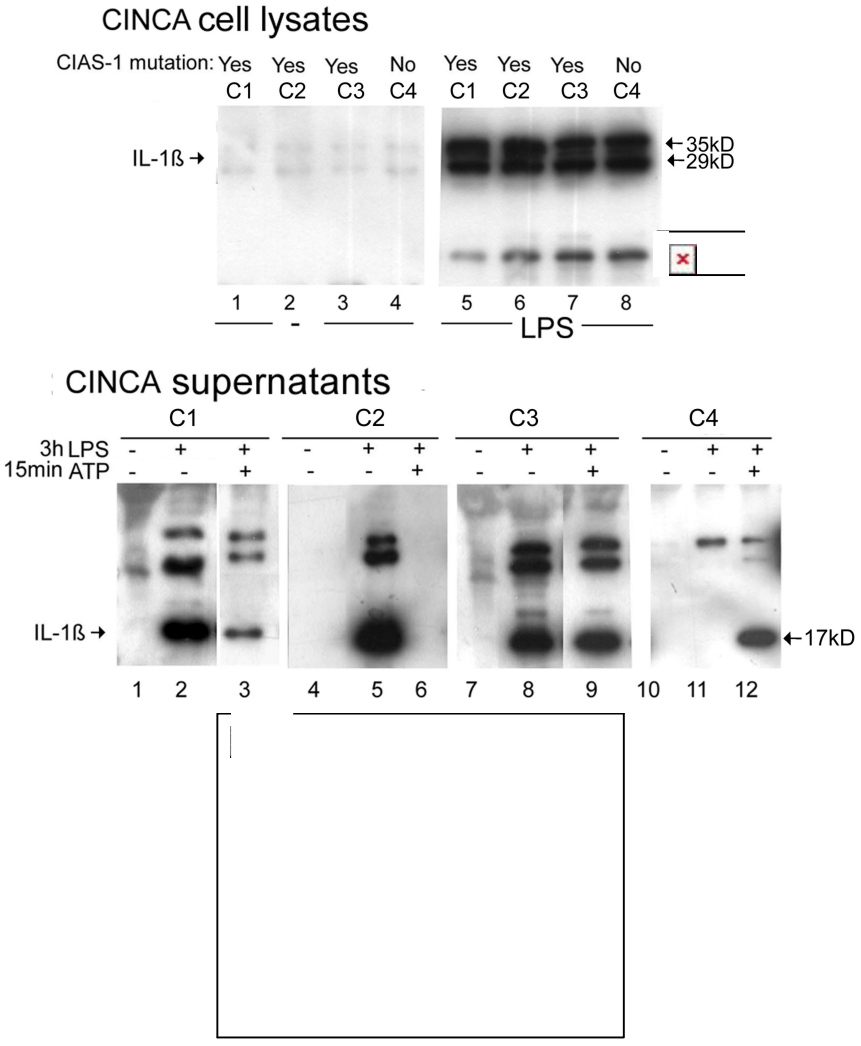


Variable response of sJIA to IL-1Ra

Gattorno et al Arthritis Rheum 2008; 58:1505-1515

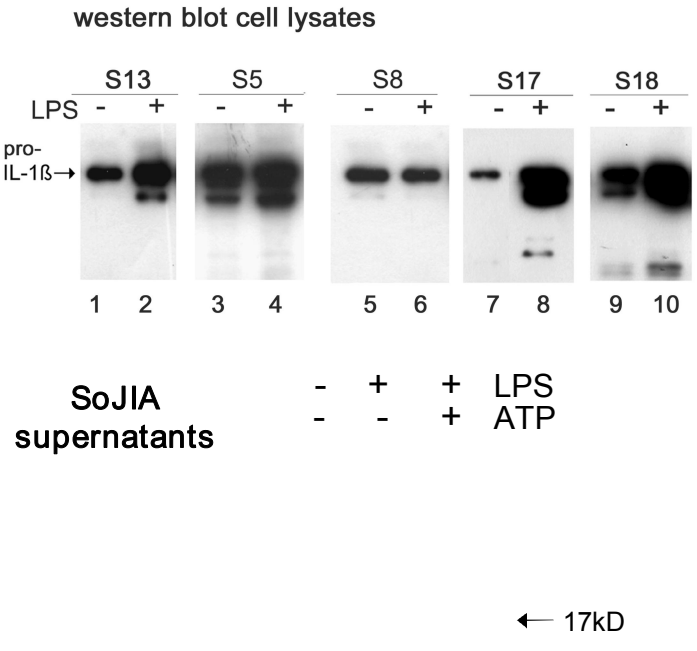
SoJIA patients do not display hypersecretion of IL-1β independently from the response to Anakinra

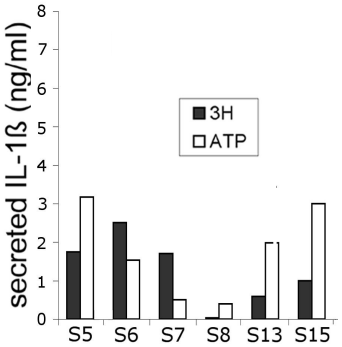
CINCA



(Gattorno et al, Arthritis Rheum 2007; 56:3138)

SoJIA





(Gattorno et al, Arthritis Rheum 2008; 58:1505)

Classification of juvenile idiopathic arthritis (Durban 1997)

- Systemic 15%
- Oligoarthritis: 50%
  - a) persistent
  - b) extended
- Polyarthritis (RF positive) 3%
- Polyarthritis (RF negative) 17%
- Psoriatic arthritis 5%
- Enthesitis related arthritis 10%

Are some forms of sJIA autoinflammatory diseases?

- It appears that treatment with IL-6 and IL-1 inhibitors will represent a very important advance in the treatment of systemic JIA and an opportunity to unravel the clinical heterogeneity of this disease.