

Juvenile Idiopathic Arthritis Treatment



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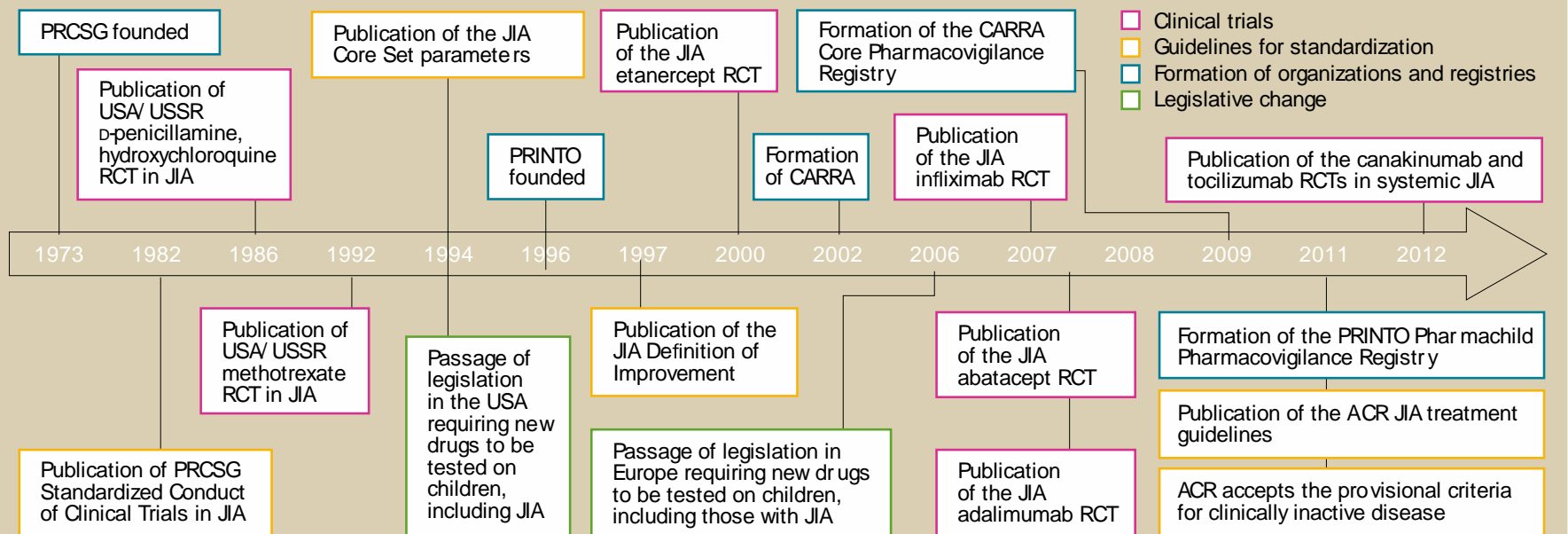
www.unesp.br

Evidence

- Prince FHM, Otten MH, van Suijlekom-Smit LWA Diagnosis and management of juvenile idiopathic arthritis. **BMJ 2010, 341: c6434.**
- Beukelman TL, Patkar NM, Saag KG et al. 2011 ACR recommendation for the treatment of JIA: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. **Arthritis Care Res 2011, 63: 465-482.**
- Ringold S, Weiss PF, Beukelman T et al. 2013 update of 2011 ACR recommendation for treatment of juvenile idiopathic arthritis: medical therapy of children with systemic JIA and tuberculosis screening. **Arthritis Care Res (Hoboken) 2013, 65:1551-1563.**
- Lovell DJ, Rupero N, Giannini EH, Martini A Advances from clinical trials in juvenile idiopathic arthritis. **Nat Rev Rheumatol 2013, 9: 557-563.**
- Zhao Y, Wallace C Judicious use of biologicals in juvenile idiopathic arthritis. **Curr Rheumatol Rep 2014, 16: 454 DOI 10.1007/s11926-014-0454-3.**
- Hinze C, Gohar F, Foell D Management of juvenile idiopathic arthritis: hitting the target. **Nat Rev Rheumatol 2015 doi 10.1038/nrrheum 2014.212.**

Timelines of JIA treatment development

Timeline 1 | Landmark dates in paediatric rheumatology*



* The timeline shows the dates of key clinical trials, guidelines, formation of organizations or registries and legislative changes that have led to advances in the management of JIA. Abbreviations: ACR, American College of Rheumatology; CARRA, Childhood Arthritis and Rheumatology Research Alliance; JIA, juvenile idiopathic arthritis; RCT, randomized, controlled trial; PRINTO, Pediatric Rheumatology International Trials Organization; PRCSG, Pediatric Rheumatology Collaborative Study Group; USSR, Union of Soviet Socialist Republics.

Lovell DJ et al. Advances from clinical trials in juvenile idiopathic arthritis.

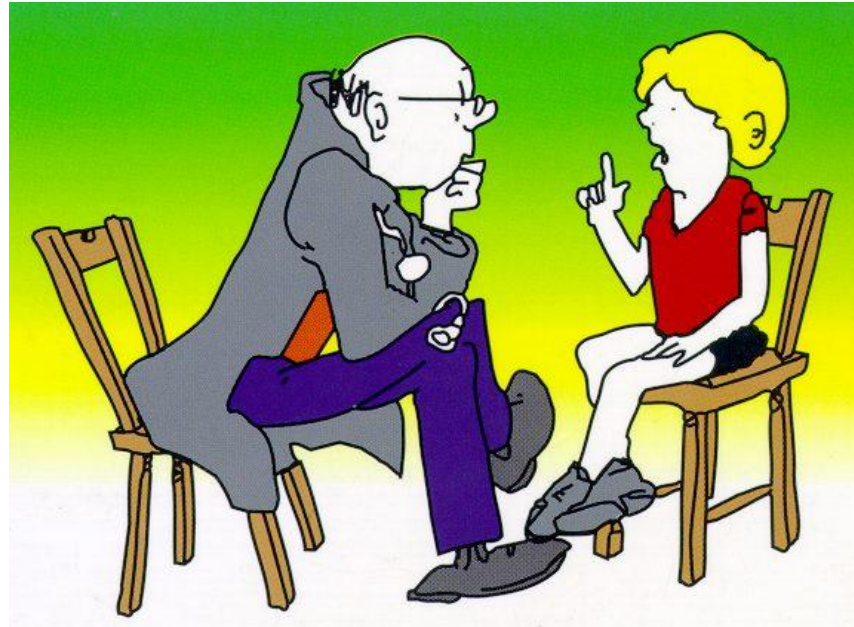
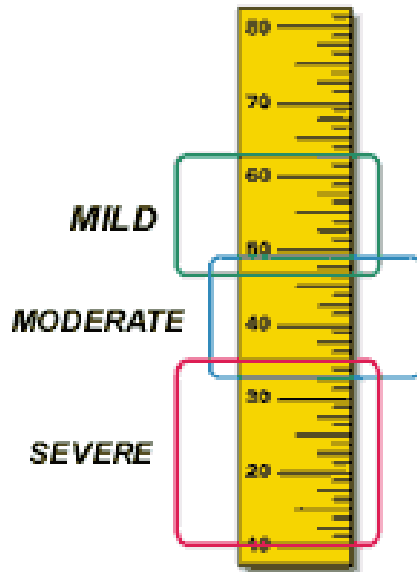
Nat Rev Rheumatol 2013, 9: 557-563.

Stoll ML, Cron RQ Treatment of juvenile idiopathic arthritis: a revolution in care. Pediatric Rheumatology 2014, 12:13

Response to treatment measures

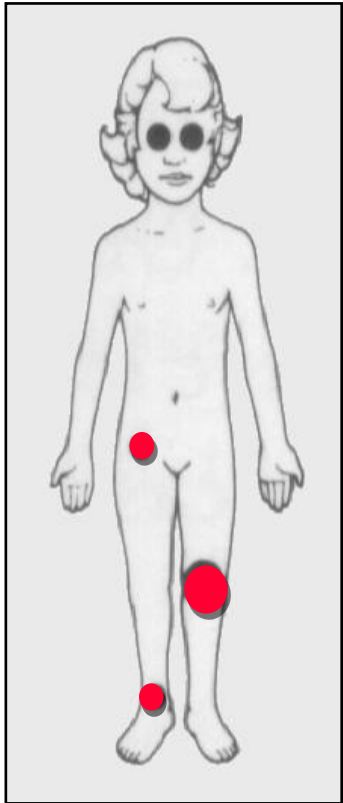
ACR- Pedi 30 defines a minimum response:

≥ 30% improvement in 3 of 6 core set variables and
no more than 1 variable worsening ≥ 30%.

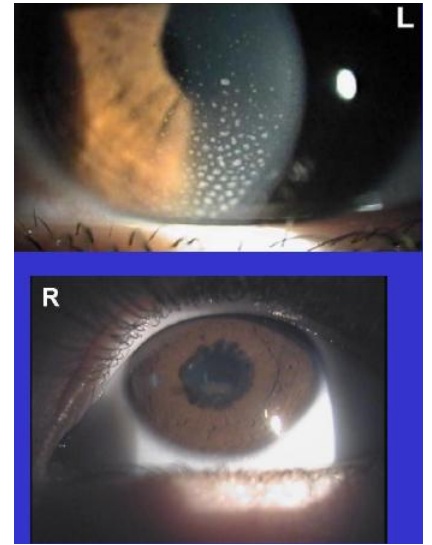
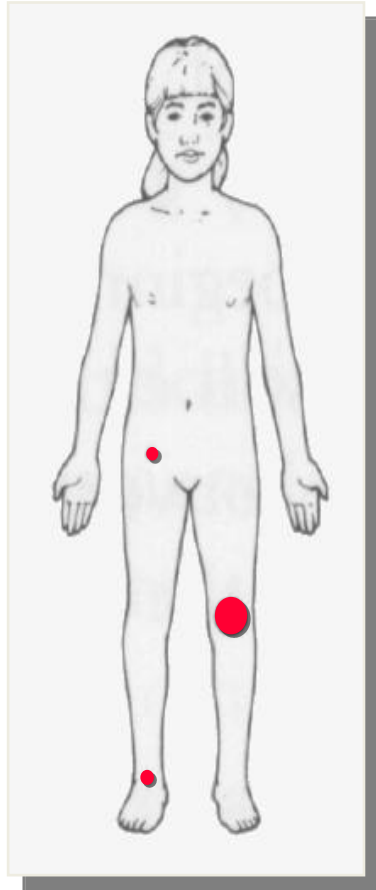


Giannini ER , Ruperto N, Ravelli A et al. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 40: 1202-9, 1997.

Oligoarticular Juvenile Idiopathic Arthritis



J Jacobs, 1993

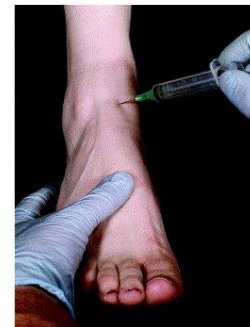
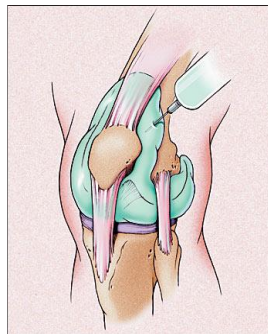


ANA + association HLA B1, B8
Uveitis Risk

Joint steroid injection

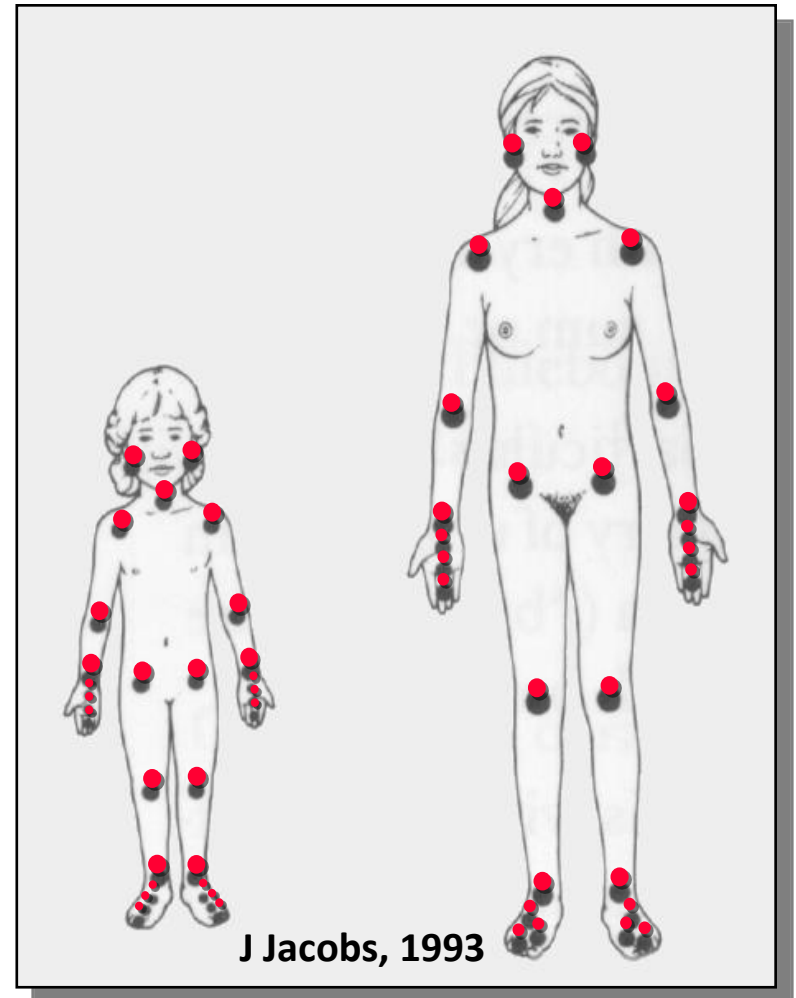


- NSAIDs
(Symptomatic treatment)
Pain relief
- Naproxen
- Diclofenac



Zulian F et al. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double blind trial. Rheumatology 2004, 43: 1288-1291.

Polyarticular Juvenile Idiopathic Arthritis



Positive Rheumatoid Factor– Negative Rheumatoid Factor
Positive ANA – Negative ANA
Proliferative Symetric Synovitis

METHOTREXATE

Dosage

Oral, SC or IM

Adverse Events

10 -15 mg/m²/wk

oral or parenteral
(IM or SC)

Response

3-6 months



30-40%

Response Failure

Oral – up to 15 mg

Parenteral
(SC or IM)
doses >15 mg

Folic Acid (Folinic)

1mg/day

5- 6 times /wk

Mild:

Oral Ulcers,

Alopecia

Gastritis

Transaminase increase

Severe:

Cytopenia

Liver toxicity

Interstitial pneumonia

Methotrexate Dose-Response

- **Oral MTX**

Double-blind trial of 5 mg/m²/wk and 10 mg/m²/wk versus PLACEBO

Giannini EH et al. New Eng J Med 1992, 326: 1043 -1049

- **SC or IM MTX**

Controlled dose-response trial comparing oral MTX and parenteral MTX (SC or IM) escalating in a double-blind comparison of high and intermediate doses

Efficacy was reached with 15 mg/m²/wk (Maximum 20 mg/wk)

Ruperto et al. Arthritis Rheum 2004, 50: 2191-2201.

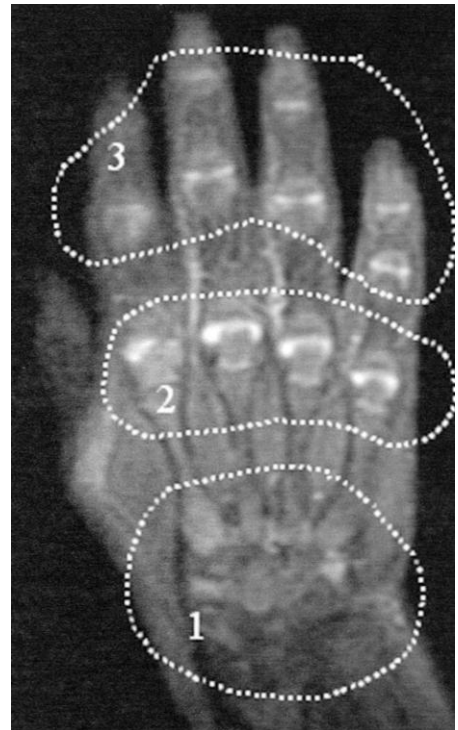
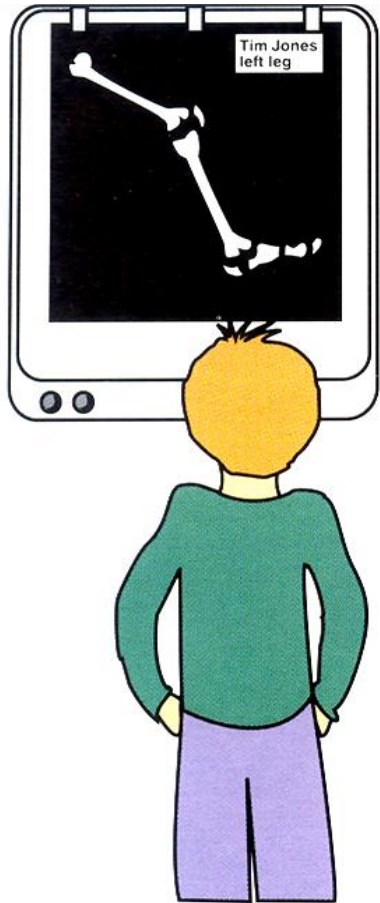
- **LEFLUNOMIDE or MTX**

“Double-dummy” trial (blind) comparing Leflunomide or Methotrexate during 16 weeks and 32 weeks blind extension.

ACR Pedi 30 response to both, but MTX efficacy was higher than leflunomide

Silverman E et al. New Eng J Med 2005, 352: 1655- 1666.

Growth Impact



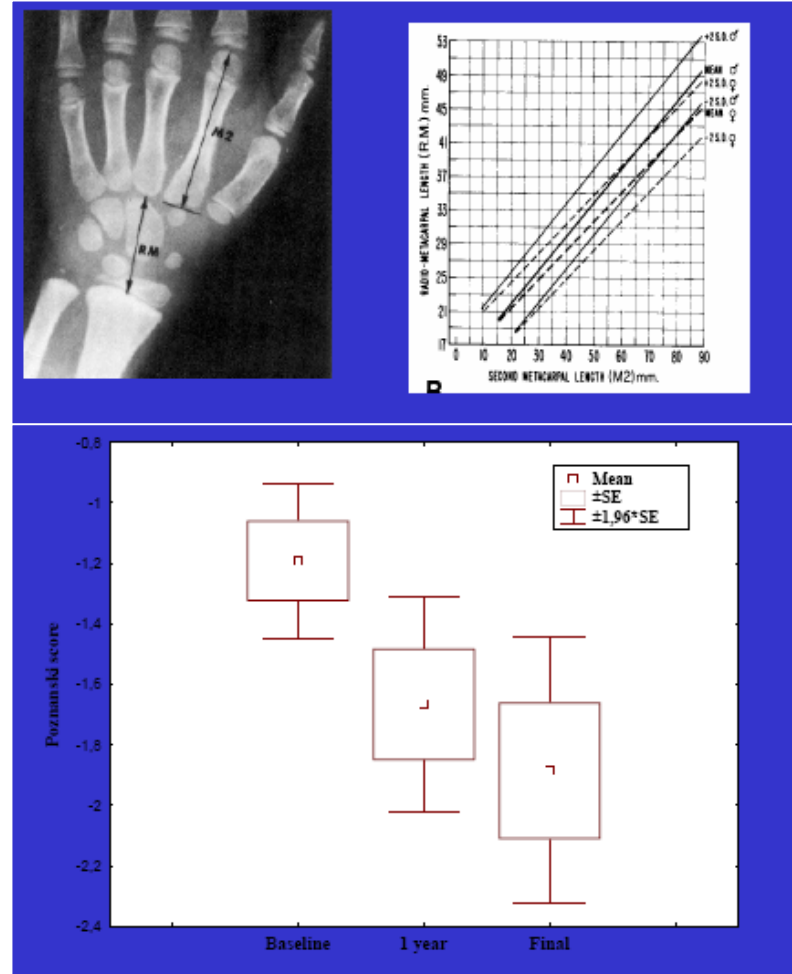
Methotrexate response in 60-70%

Growth Impact

POZNANSKI INDEX

The measure of proportional relationship of the length of the second metacarpal bone correlates with height and linear bone growth: a good measure of arthritis progression.

In the first year of treatment with METHOTREXATE this index is a good predictor of function and limitation due to Polyarticular JIA.



Methotrexate safety and long term outcome

- **Safety and Adverse Events Monitoring**

Gastro-intestinal adverse events, liver toxicity and folate supplementation.

Lahdenne P et al. J Rheumatol 2002, 29: 2442-65.

Ortiz-Alvarez O et al. J Rheumatol 2004, 31: 2501-2506.

Kocharla L et al. J Rheumatol 2009, 36: 2813-2818.

- **Magnitude of response and long term outcome**

- Time of treatment onset: **Early treatment results in better outcome**

Bartoli M et al. Ann Rheum Dis 2008, 67 370-374.

Albers HM et al. Arthritis Rheum 2009, 15: 46-51.

- **Timing withdrawal when JIA attains clinical remission**

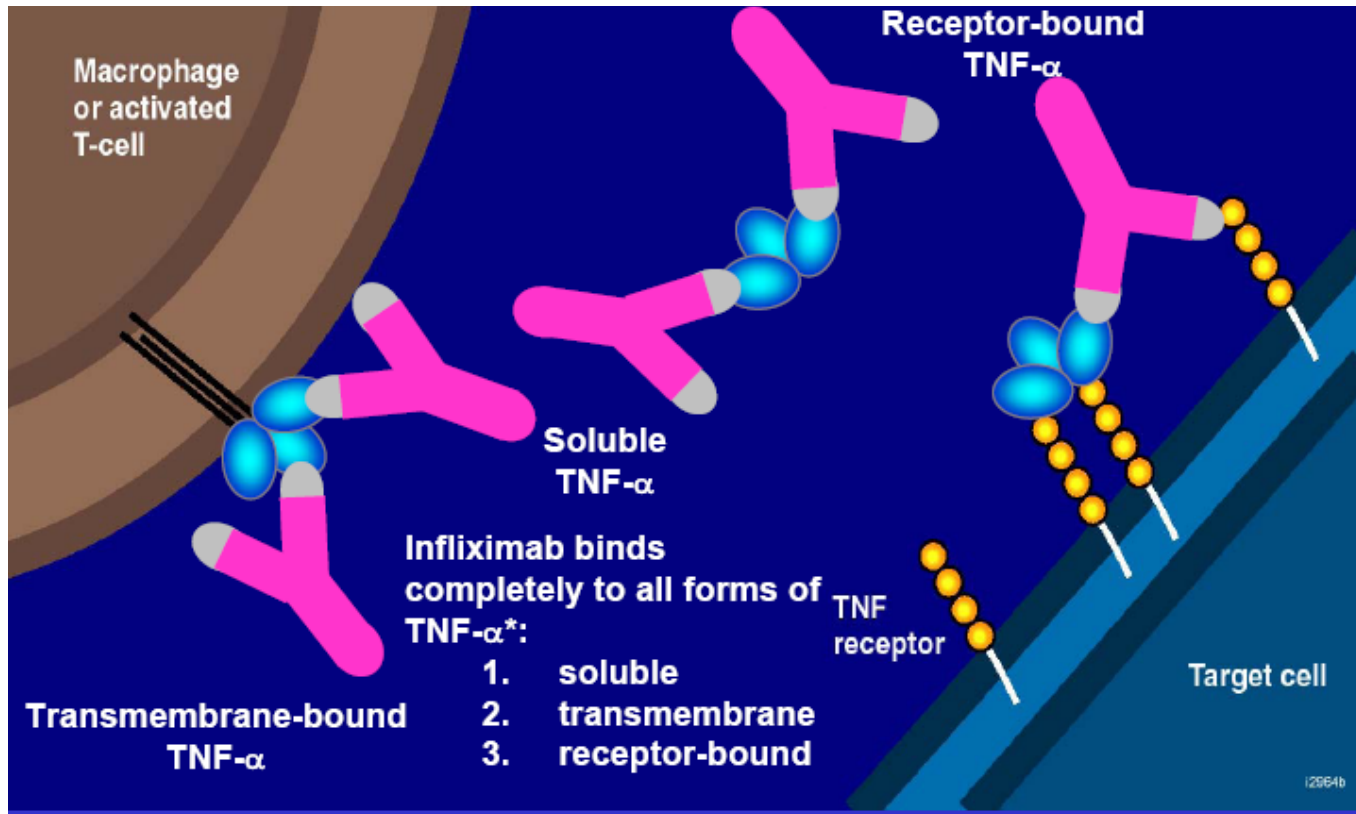
Foell D et al. JAMA 2010, 303: 1266-1273.

- **Biomarkers and outcome predictors**

van Dijkhuizen EHP, Wullfraat N Pediatric Rheumatology 2014, 12: 51.

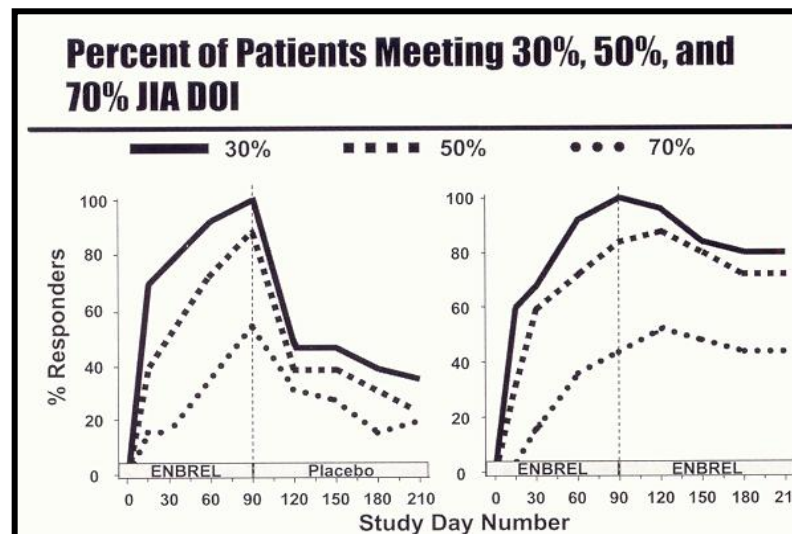
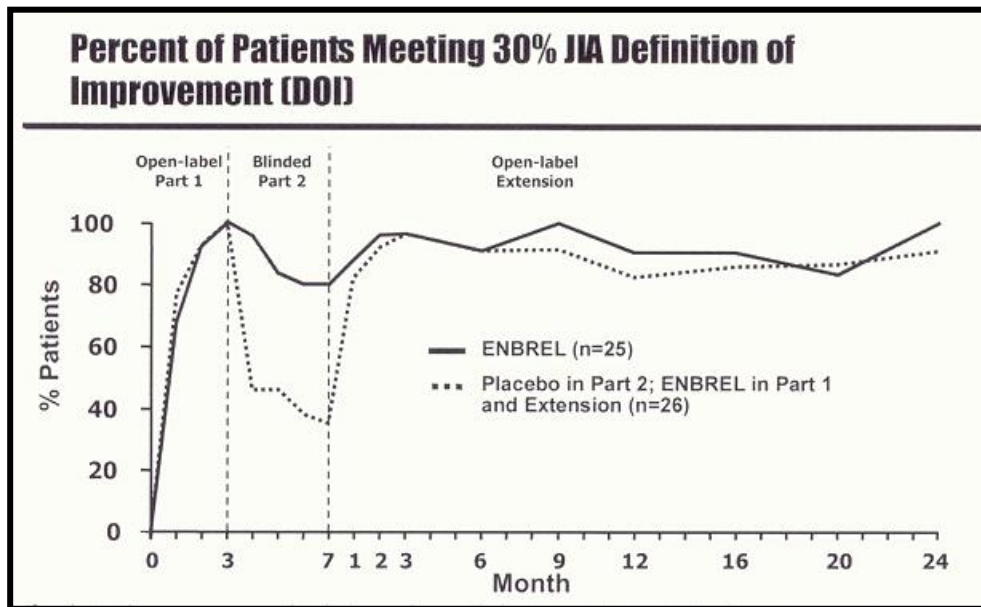
Hinze C et al. Nat Rev Rheumatol 2015, doi 10.10308/nrrheum.

Anti-TNF Treatment: Mechanism of Action



Knight DM et al. Mol Immunol 1993; 30(16): 1443-53

ETANERCEPT the first biologic agent tested in a withdrawal design

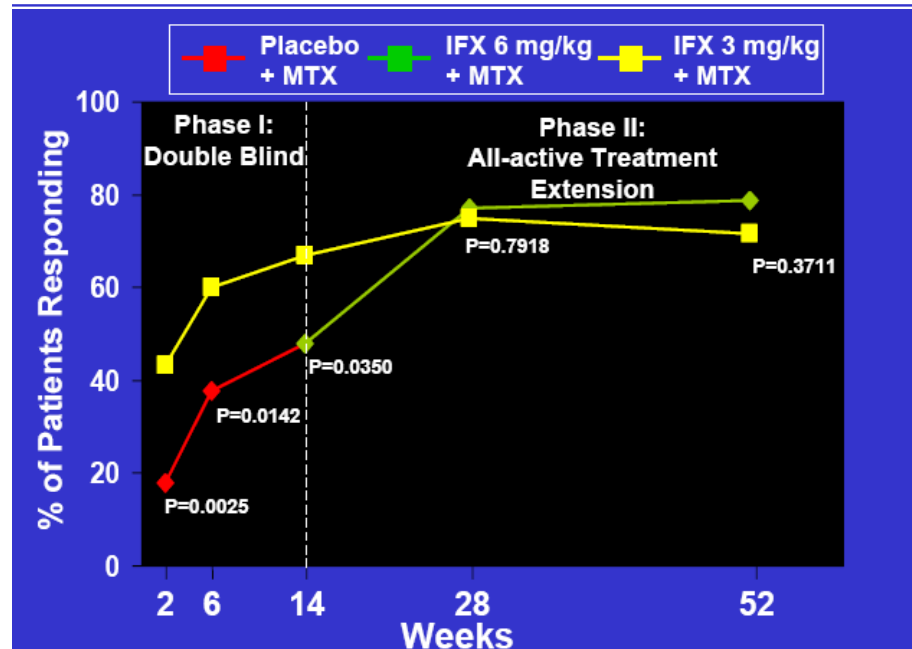


Lovell DJ et al. N Engl J Med 2000, 342:763-769.

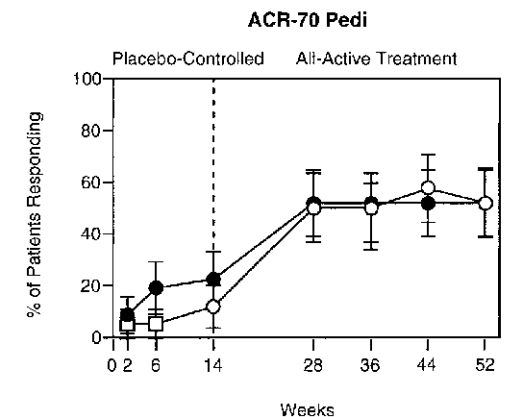
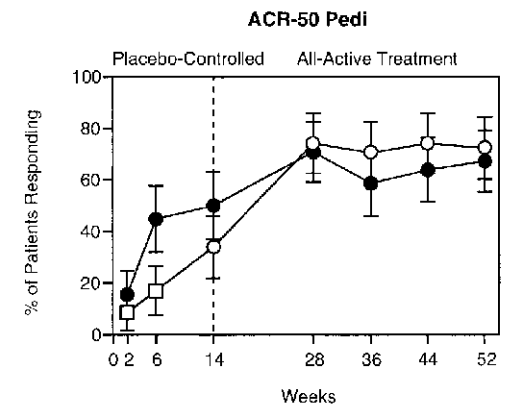
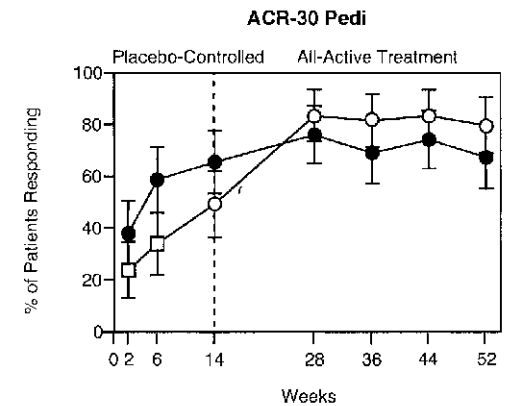
Lovell DJ et al. Arthritis Rheum 2003, 48: 218-226.

Lovell DJ et al. Arthritis Rheum 2008, 58: 1496-1504.

INFLIXIMAB and METHOTREXATE versus PLACEBO in POLYARTICULAR JIA



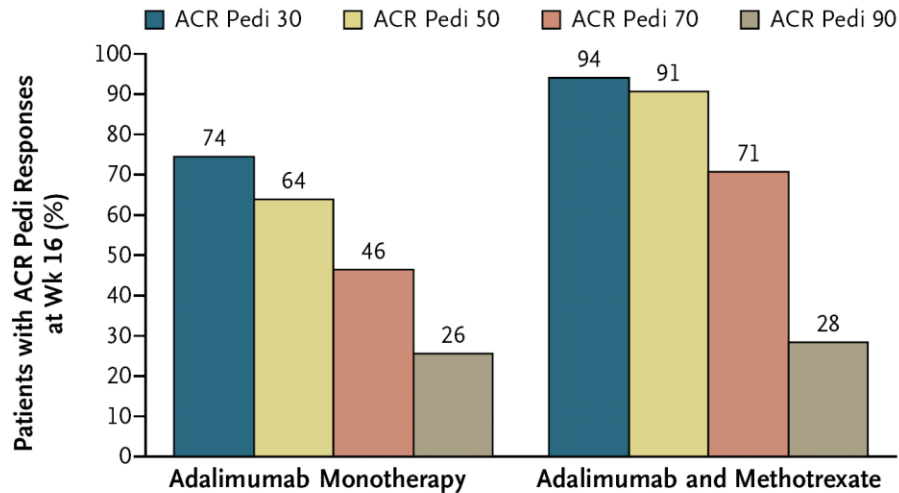
Ruperto N et al. Arthritis Rheum 2007, 56: 3096-3106.
Ruperto N et al. Ann Rheum Dis 2010, 69: 718-722



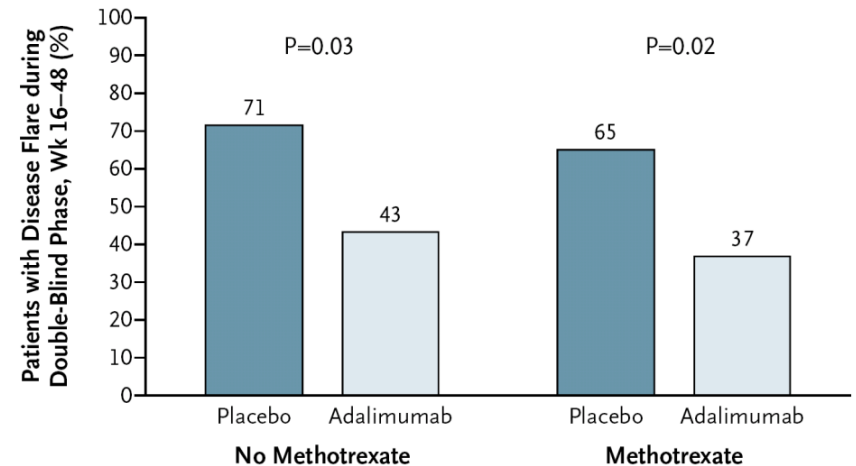
□ Placebo + MTX
○ Infliximab 6 mg/kg + MTX
● Infliximab 3 mg/kg + MTX

Adalimumab and Methotrexate Efficacy

A



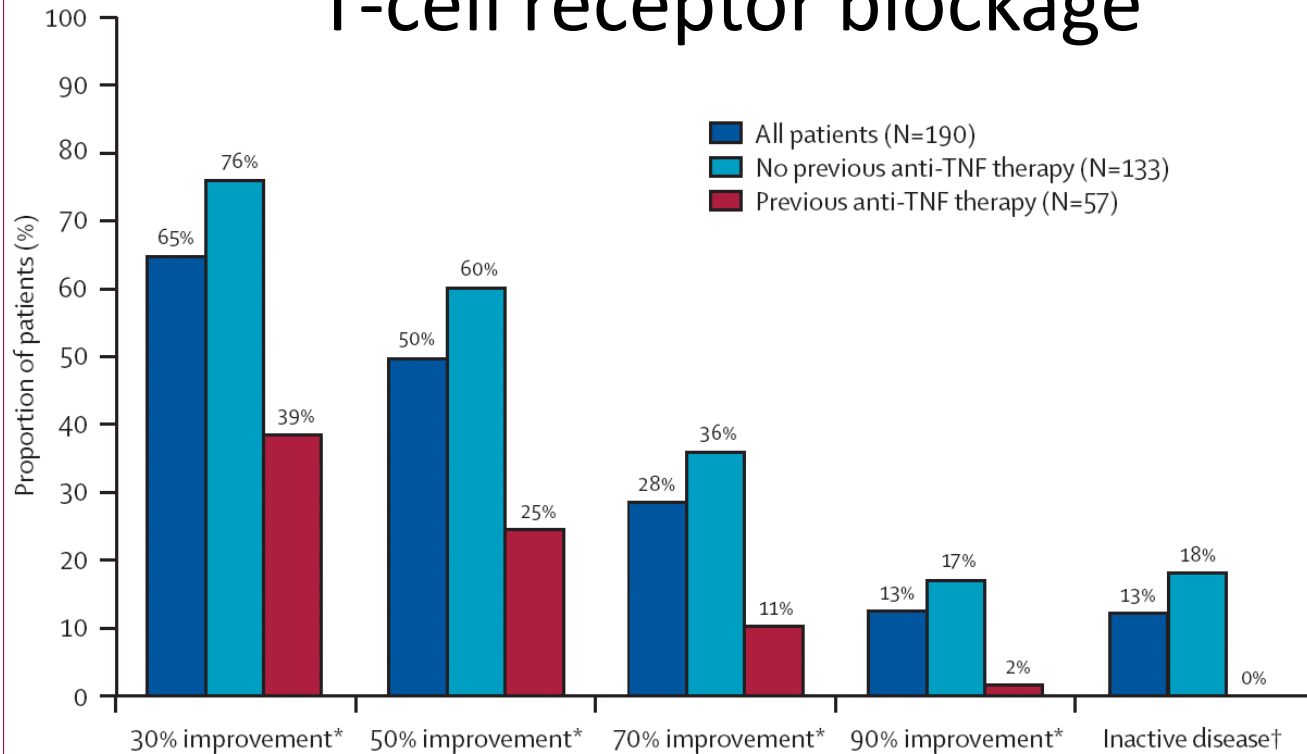
B



Lovell DJ et al. NEJM 2008; 359: 810-820.

Abatacepte Efficacy

T-cell receptor blockage



Ruperto N et al. Lancet 2008, 372: 393-391.

Ruperto N et al. Arthritis Rheum 2010, 62: 1542-1551.

Ruperto N et al. Arthritis Rheum 2010, 62: 1792-1802.

Lovell DJ et al. Arthritis Rheum (unpublished)

Enthesitis Related Arthritis

Ankilosing Spondylitis

Reactive Arthritis

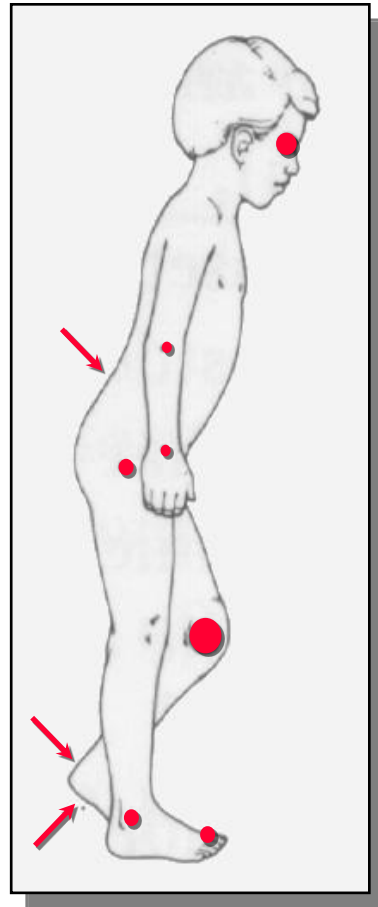
Inflammatory Bowel
Disease related
arthritis

Psoriatic Arthritis

Anterior Uveitis

HLA-B27

Undifferentiated Arthritis

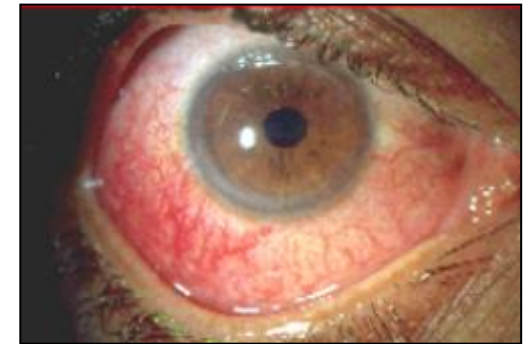
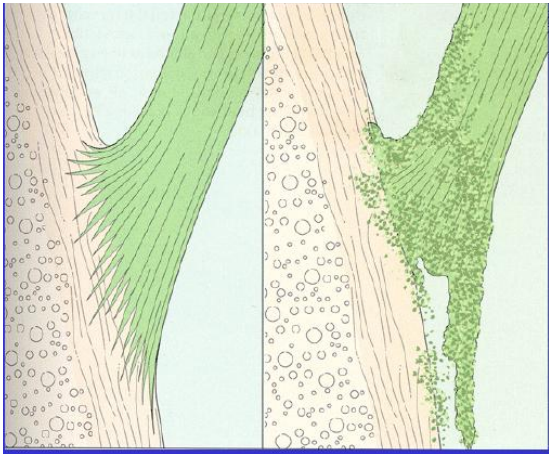


***... A rose by any other name is still a
rose. WS***

Colbert RA Classification of juvenile spondyloarthritis, enthesitis- related arthritis and beyond.

Nature Reviews-Rheumatology 2010, 6: 477-485.

Enthesitis Related Arthritis Treatment

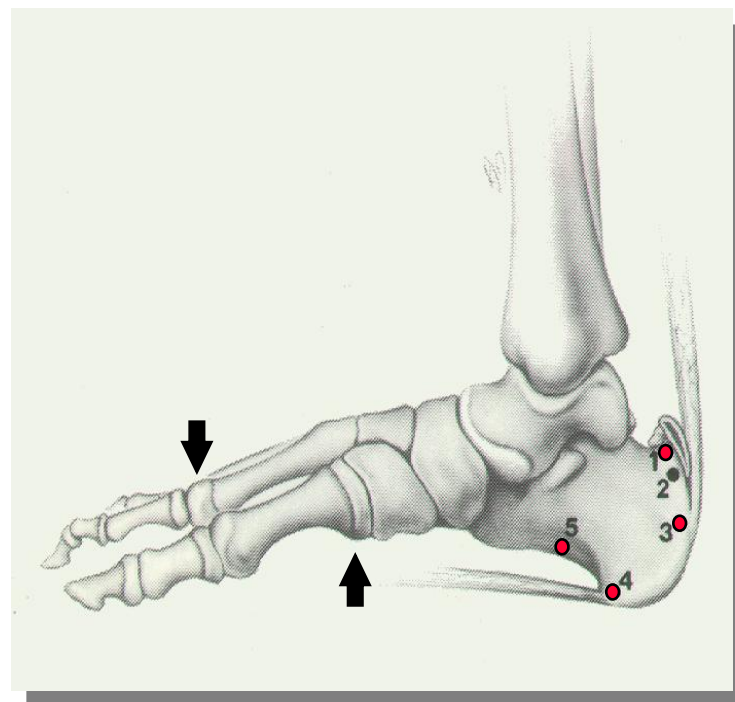
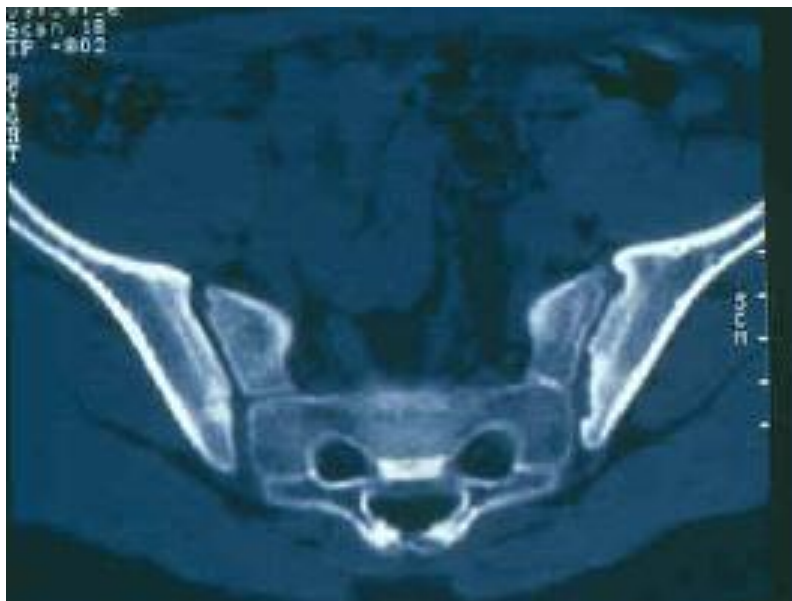


- ETANERCEPT, Horneff G et al. Ann Rheum Dis 2014, 73: 1114-22. (CLIPPER)
- ADALIMUMAB Horneff G et al. Arthritis Res Ther 2012, 14: R230

Enthesitis and Spine Involvement



Burgos-Vargas R, Clark P Axial involvement in the seronegative enthesopathy and arthropathy syndrome and its progress to ankylosing spondylitis. J Rheumatol 1989, 16: 192-197

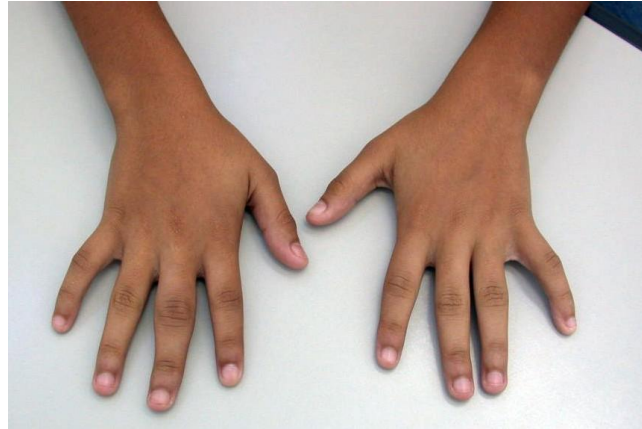


USTEKINUMAB –IL-23 blockage experimental evidence / “TOPAS” trial Anti IL12/23

Sherlock JP et al. Nat Med 2012, 18: 1069-76

Poddubnyy D et al. Ann Rheum Dis 2014, 73: 817-823

Psoriatic Arthritis



* CLIPPER study: First trial with anti-TNF for extended oligoarticular, psoriatic and enthesitis related arthritis

Horneff G et al. Ann Rheum Dis 2014, 73: 1114-22.

Uveitis Treatment



Refractory Uveitis Treatment

- Prednisolone (topic plus midriatics)
- Prednisolone (oral) short course*
- Methotrexate

Foeldvari I et al. J Rheumatol 2007, 34: 1146-1150.

Papadopoulo C et al. J Pediatr 2013, 163: 879-884.

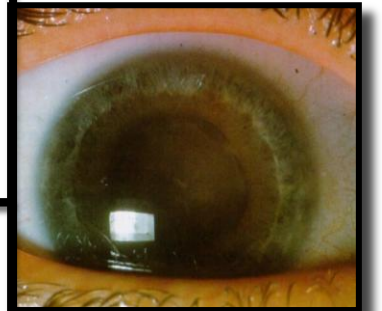


- Etanercept

Reiff A Arthritis Rheum 2003, 48: 2079-80

- Infliximab and Adalimumab

Sukumaran S et al. ISRN Rheumatology 2012: 765380



- Abatacept

Kenawy N et al. Graefes Arch Clin Exp Ophthalmol 2011, 249: 297-300.

Zulian F et al. Arthritis Care Res 2010, 62: 821-825.

- Tocilizumab

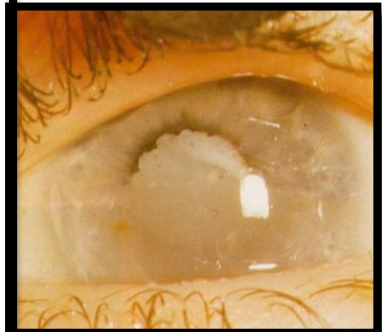
NCT 01603355 e NCT 01717170

- Micofenilato Mofetil

Sobrin L et al. Ophtalmology 2008, 115: 1416-1431

- Rituximab

Helinghaus A et al. Rheumatology 2011, 50: 1390-1394.



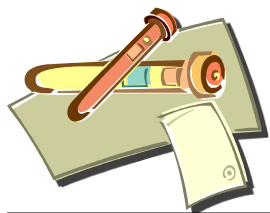
Practical Guidelines and Recommendations

	Australia	Germany	UK and Ireland	United States	United States
YEAR	2009	2011	2001-2011	2011	2013
LITERATURE	2000-2007	up to 2010	-	1966-2009	up to 2013
METHOD	Literature review e-mail circulation	Systematic review Delphy and Nominal consensus techniques	Informal Consensus	Systematic Review RAND/UCLA model Task force/Expert Pannel	Systematic Review RAND/UCLA model Task force/Expert Pannel
TARGET	Primary care	Pediatric Rheumatol	Generalist	Pediatric Rheumatol	Pediatric Rheumatol

Hull R et al. (BSPAR) Rheumatology 2001, 40: 1309-1312; Davies K et al. (BSPAR) Rheumatology 2010, 49: 1406-1408; Dueckers G et al. Clin Immunol 2012, 142: 176-193; Beukelman T et al Arthritis Care Res 2011, 63: 465-482; Ringold S et al. Arthritis Care Res 2013, 66: 1063-1072.

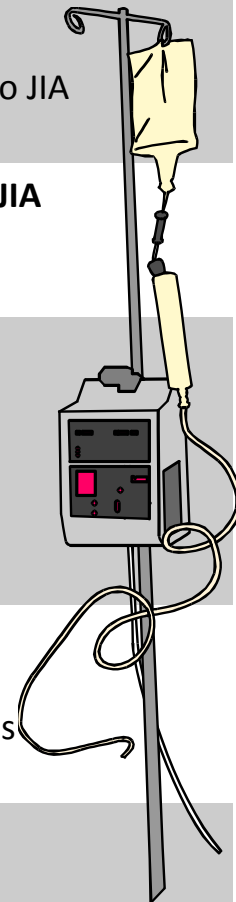
DMARDS – Disease modifying agents

Agent	Dose	It can not be used	Adverse Event
METHOTREXATE	10-15 mg/m ² /WK oral, SC (max 25 mg/m ²)	Liver dysfunction, renal, dyserythropoiesis, active infection, pregnancy and lactancy	Nausea, vomits, anorexia, transaminase increase, myelodysplasia, theratogenesis
SULFASALAZINE	50mg/Kg/day 2-3 daily doses (max 2g/day)	Allergy, salicylates, sulpha, Systemic JIA	Allergic reactions, GI intolerance, myelodysplasia
LEFLUNOMIDE	<ul style="list-style-type: none"> <20Kg: 100mg 1 day/10 mg alt days 20-40 Kg: 200 mg 2 days 10mg/day >40 Kg: 100 mg 3 days 20 mg/day 	Immunodeficiency, dyserythropoiesis, active infection, liver failure, low albumin, pregnancy and lactancy	GI symptoms, allergic reactions, high transaminases, abnormal blood cell count, theratogenesis
CYCLOSPORIN	3-7 mg/Kg/day oral or IV	Renal Failure, Hypertension, Infection	Hypertension, Renal Toxicity, Ca and Mg depletion, cramps, hirsutism, gum hypertrophy, PRES, encephalopathy



The choice of biologic treatment– Anti- TNF

Agent	Action	Dosis	Indication
ETANERCEPT*	TNF alpha receptor fusion protein	0,4 mg/Kg 2 times /wk 0,8 mg/Kg/wk SC SC max 50 mg/wk	Polyarticular JIA Extended Oligo JIA Rarely Persistent Oligo JIA Plaque Psoriasis
ADALIMUMAB*	Human Monoclonal antibody to TNF	<30 Kg 20 mg / 2 wk >30 Kg 40 mg/ 2 wk SC	Polyarticular Course JIA Crohn's Disease Ulcerative Colitis
INFLIXIMAB	Chimeric (rat/human) Monoclonal antibody to human TNF	6-10 mg/Kg IV 0,2 and 6 wks, every 4-8 wks Uveitis: doses up to 20 mg/Kg	Rheumatoid Arthritis Crohn's Disease Ulcerative Colitis Plaque Psoriasis UVEITIS
GOLIMUMAB	Human Monoclonal antibody to TNF	Pediatric doses not yet identified (50 mg every 4 wks) SC NCT 01230827	Rheumatoid Arthritis Psoriatic Arthritis Ankylosing Spondylitis
CERTOLIZUMAB-PEGOL	Human Monoclonal antibody to TNF Fab - PEG	Pediatric doses not yet identified RA 400 mg 0,2,4 wk, 200 mg/2 wk or 400mg/4 wks SC NCT 01550003	Rheumatoid Arthritis



Anti-TNF Risks of Adverse Events

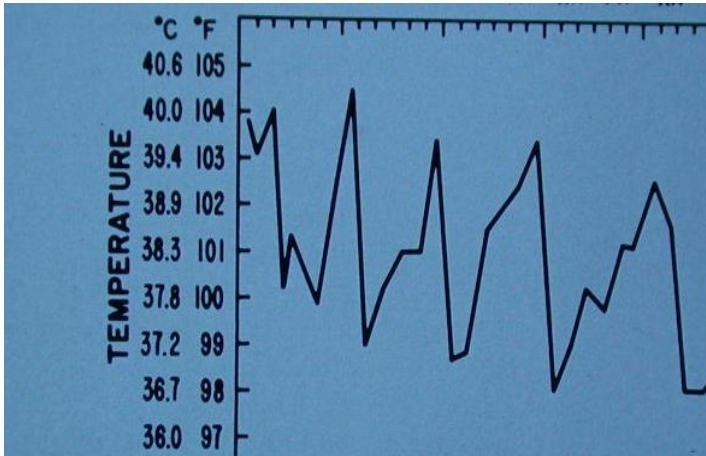
- Latent tuberculosis reactivation, other opportunistic infections
- Demyelinating diseases: onset or exacerbation of previous disease
- Auto-antibodies development (ANA, anti-DNA, a-CL)
- Autoimmune phenomena and autoimmune diseases(lupus-like)
- Infusion and post-infusion reaction (Infliximab)
- Heart Failure worsening
- **Malignancy increased incidence**

REQUIRES LONG-TERM PHARMACOVIGILANCE

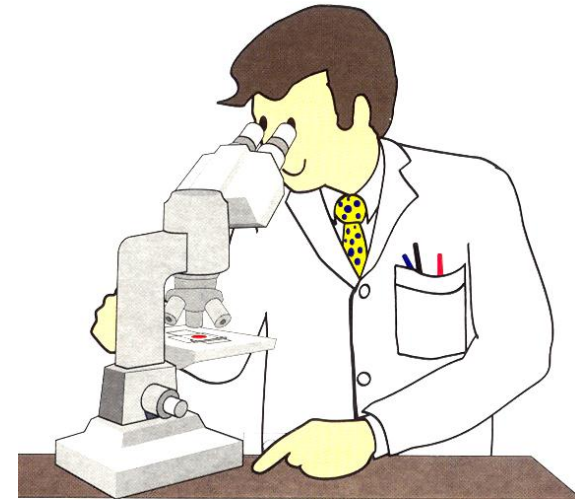


Systemic Arthritis

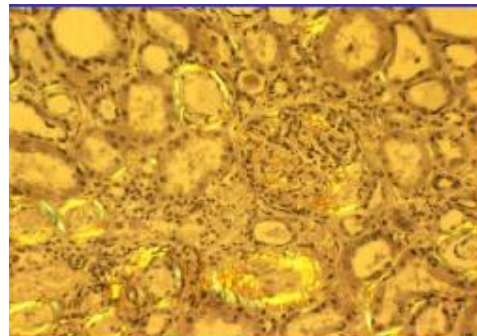
High spiking fever



Evanescent rash



Serositis



Amyloidosis

- WBC count and neutrophils
- Platelets
- Microcytic anemia
- High ESR and CRP
- High levels of Ferritin

Systemic Glucocorticoids

Prednisone- Prednisolone- Methyl-prednisolone

- Fever, Pericarditis, Myocarditis
- Macrophage activation syndrome
- 'Bridge' for DMARD

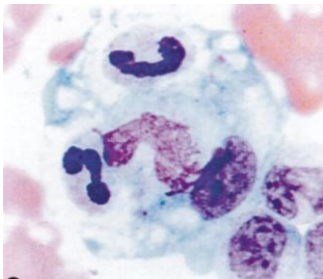


Systemic Juvenile idiopathic Arthritis

Macrophage Activation Syndrome (MAS)

REACTIVE HEMOPHAGOCYTIC LYMPHOHYSTIOCITOSIS

•
**Response to high
dose glucocorticoids
Cyclosporin A**

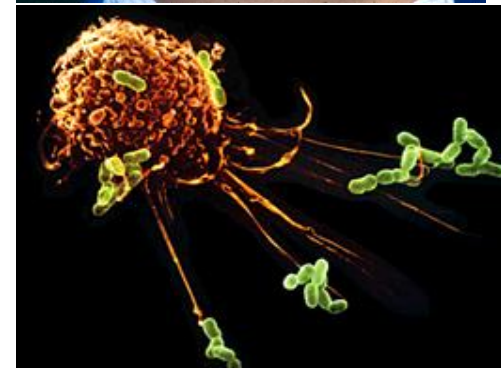
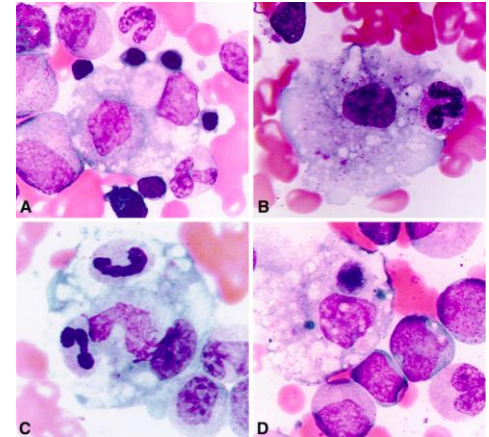


- **Cytopenia**
- Transaminase increase
- Decreased fibrinogen
- Coagulopathy
- Decreased ESR
- **Very high ferritin levels**
- Hyponatremia
- Hypoalbuminemia
- **Hemophagocytosis**

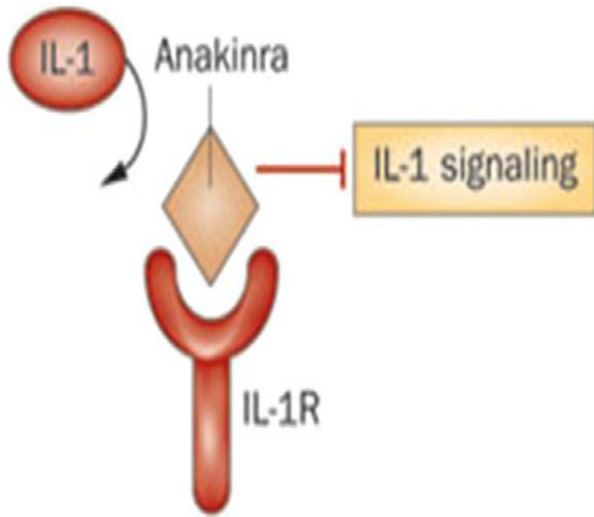
Ravelli et al. J Pediatr 1996; 128: 275-8.

Mouy et al. J Pediatr 1996; 129:750.

Grom & Passo J Pediatr 1996; 129:630.



IL-1 Receptor signaling block

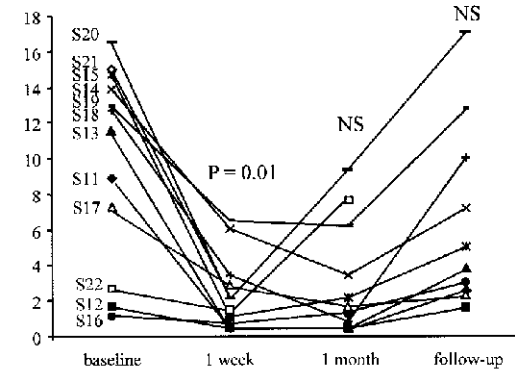
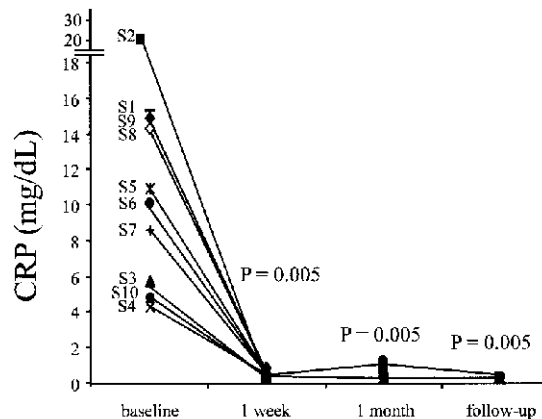
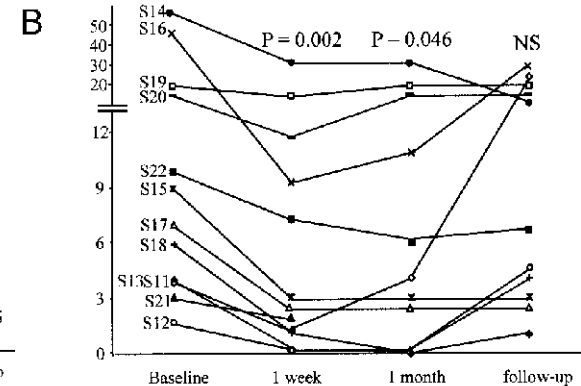
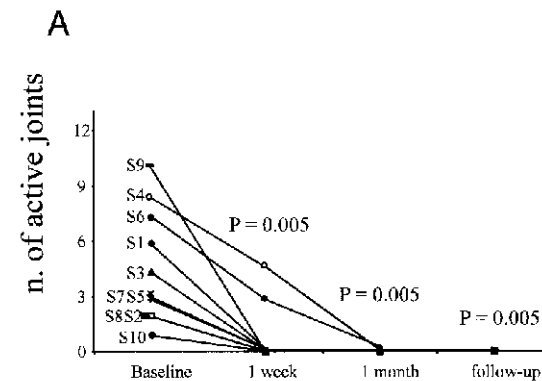


Pascual V et al. Role of IL-1 in the pathogenesis of sJIA and clinical response to IL-1. J Exp Med 2005; 201: 1479-86.

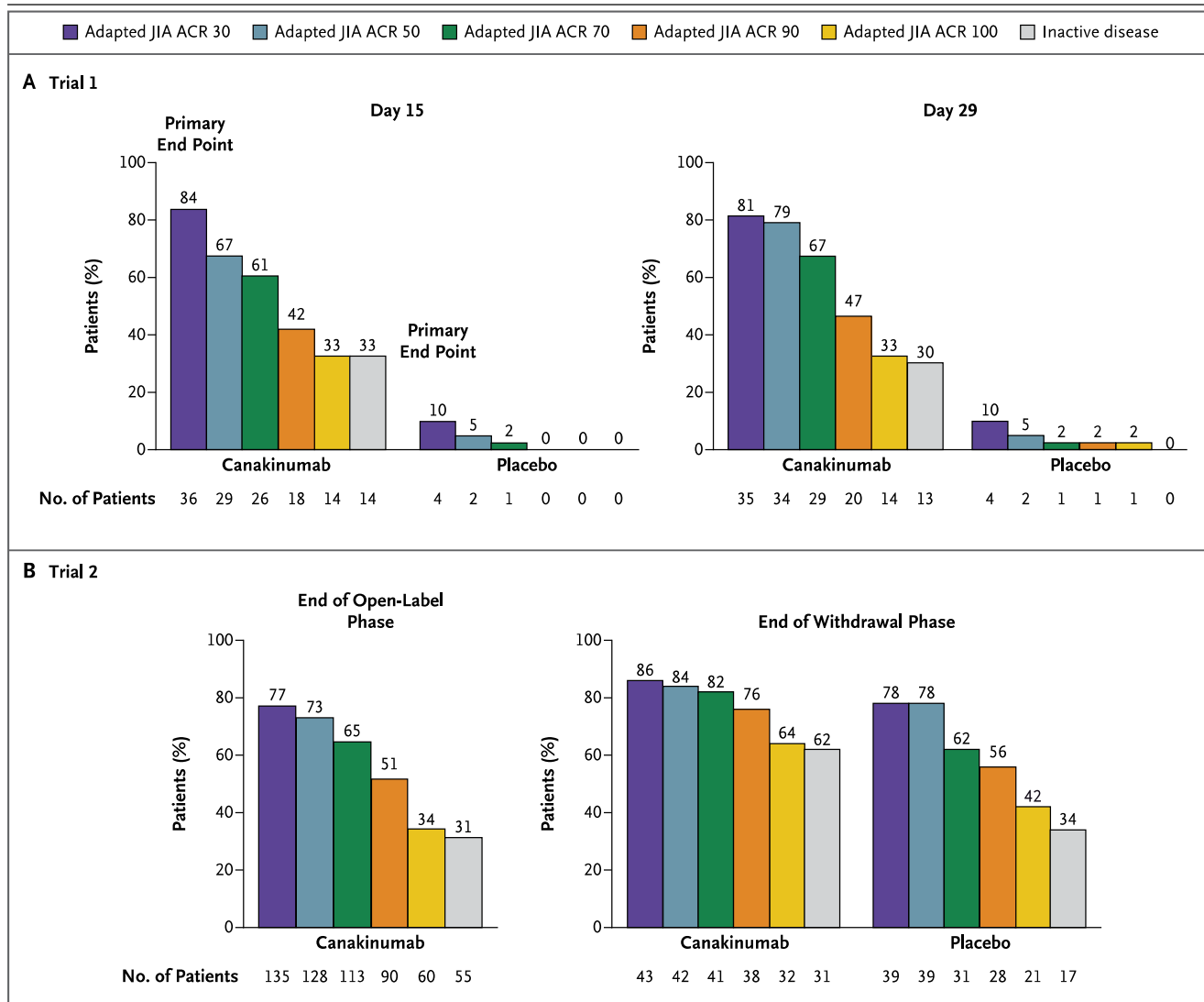
ANAKINRA: First trial about efficacy of IL1 blockage in Systemic JIA (ANAJIS)
Quartier P et al. Ann Rheum Dis 2011, 70: 747-754.

ANAKINRA: Efficacy in only 50% in open study.

Gattorno et al. Arthritis Rheum 2008, 58: 1505-1515.



Response to Canakinumab



- Ruperto N et al. Arthritis Rheum 2012, 64: 557-567.
- Ruperto N et al. New Eng J Med 2012, 367: 2396-2407.

Pathogenic role of IL-6 in Systemic JIA

SERUM AND SYNOVIAL FLUID

- De Benedetti F et al. J Clin Invest 1997, 99: 643-650.
- De Benedetti F et al. Endocrinology 2001, 142: 4818-4826.

CHRONIC

- Martini F et al.
- Gazzera C et al.

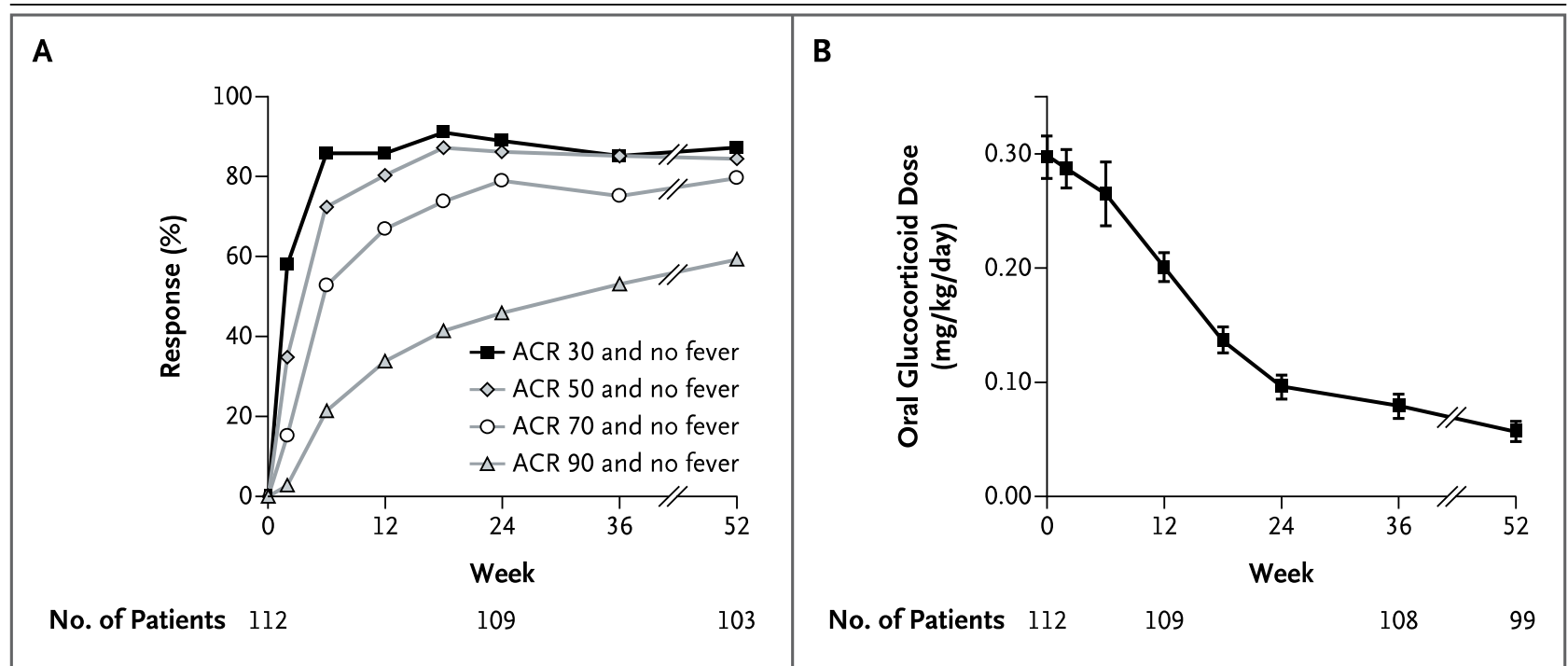
GROWTH AND DEVELOPMENT

- De Benedetti F et al. J Clin Invest 1997, 99: 643-650.
- De Benedetti F et al. Endocrinology 2001, 142: 4818-4826.
- De Benedetti F et al. J Immunol 2001, 166: 4334-4340.



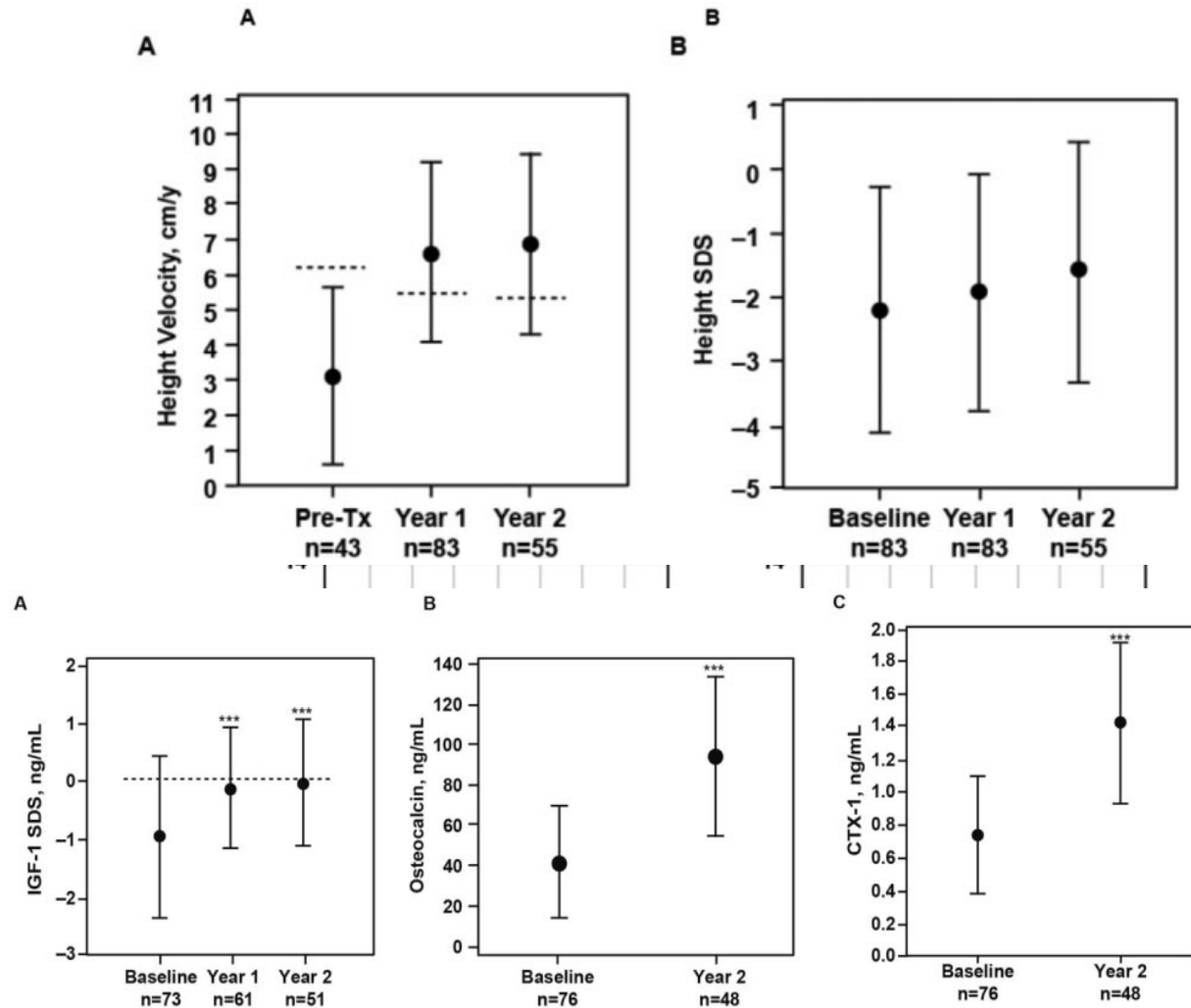
Anti-IL-6 treatment of Systemic JIA

TOCILIZUMAB IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS



De Benedetti F et al New Eng J Med 2012, 367:2385-2395.

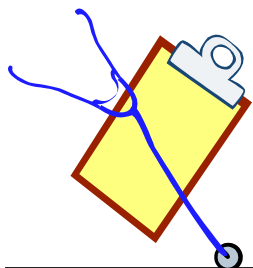
Growth and development after anti-IL6 treatment



De Benedetti F Catch up growth during tocilizumab therapy for systemic juvenile idiopathic arthritis, results of a phase III trial. Arthritis Rheum 2015, 67: 840-848.

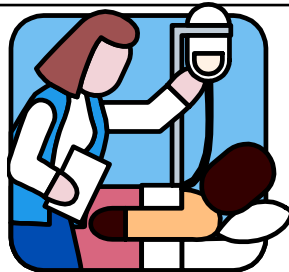
Biologic treatment: anti-IL-1, anti-IL-6

Agent	Action	Dosis	Indication
ANAKINRA	IL-1 receptor antagonist	1-2 mg/Kg/day SC Max 100 mg	Cryopirin periodic fevers
RILONACEPT	IL-1 receptor fusion protein antibody (IL 1RacP-FC)	initial Dosis 4.4 mg/ wk (max 320 mg) SC Maintenance 2.2 mg/ wk (max 160 mg) SC	Cryopirin periodic fevers
CANAKIMUMAB	Humanized human anti IL-1 beta antibody	4 mg/Kg/dosis Max 300 mg/ 4 wk SC	Cryopirin periodic fevers Systemic JIA
TOCILIZUMAB	Humanized human anti IL-6 antibody	< 30 Kg 12 mg/Kg every 2 wk > 30 Kg 8 mg /Kg every 4 wk Max 300 mg IV (SC preparation is in development) NCT 02165345	Systemic JIA CLINICAL TRIAL Macrophage activation syndrome NCT 02007239



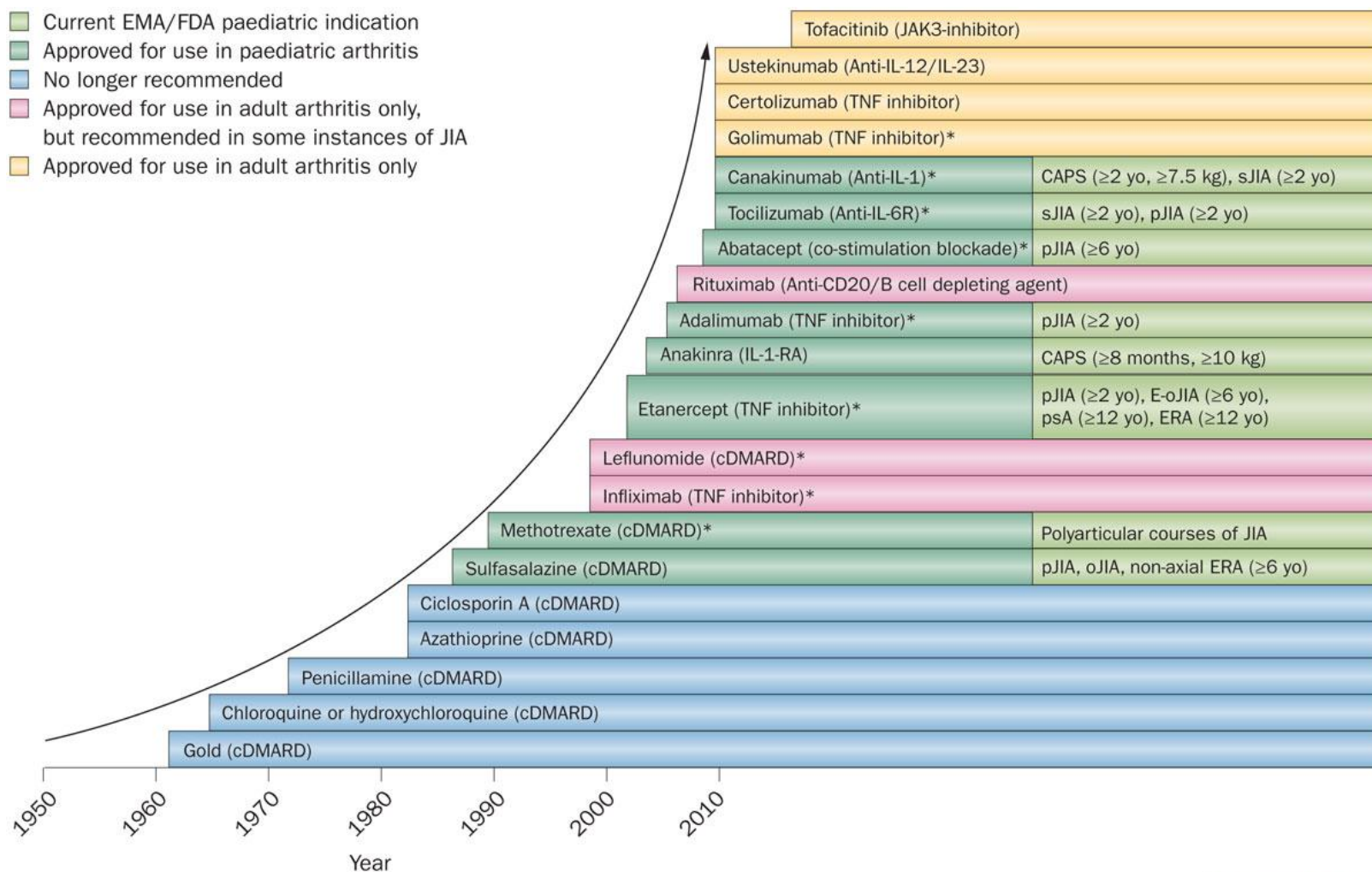
Biologic treatment– T cell selective block and B-cell depletion

Agent	Action	Dosis	Indication
ABATACEPT	co-stimulatory blockage 80/86 (CTLA4 Ag)	10 mg/Kg 0, 2, 4 and every 4 weeks (max 1000 mg) IV SC in development NCT 01844518	Polyarticular Course JIA
RITUXIMAB	Chimeric monoclonal anti-CD 20 antibody	750 mg/ m2/dosis (max 1000 mg) 2 doses in 2 weeks time IV	Non Hodgkin B-Cell Lymphoma Systemic Lupus Erythematosus Systemic JIA ** (no trial)



Zhao Y, Wallace C Curr Rheumatol Rep 2014, 16: 454-463.

Figure 1 The armamentarium of anti rheumatic drugs available for the treatment of JIA



Thank you for
early treatment



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