LABORATORY OF RESEARCH ON DIABETES « LAREDIAB »

5th SEMINARY OF LAREDIAB

11th CONGRESS OF AMIWIT

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS & ADULT-ONSET STILL'S DISEASE:TWO NAMES ONE DISEASE

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PR A,LOUNICI

The Continuum of sJIA and AOSD

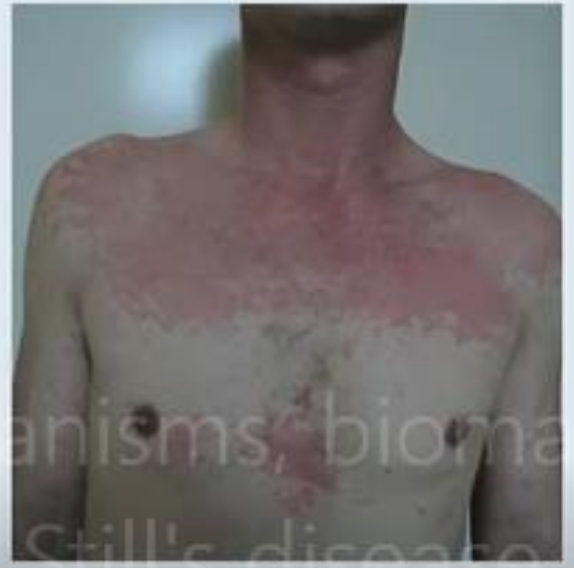
Systemic Features

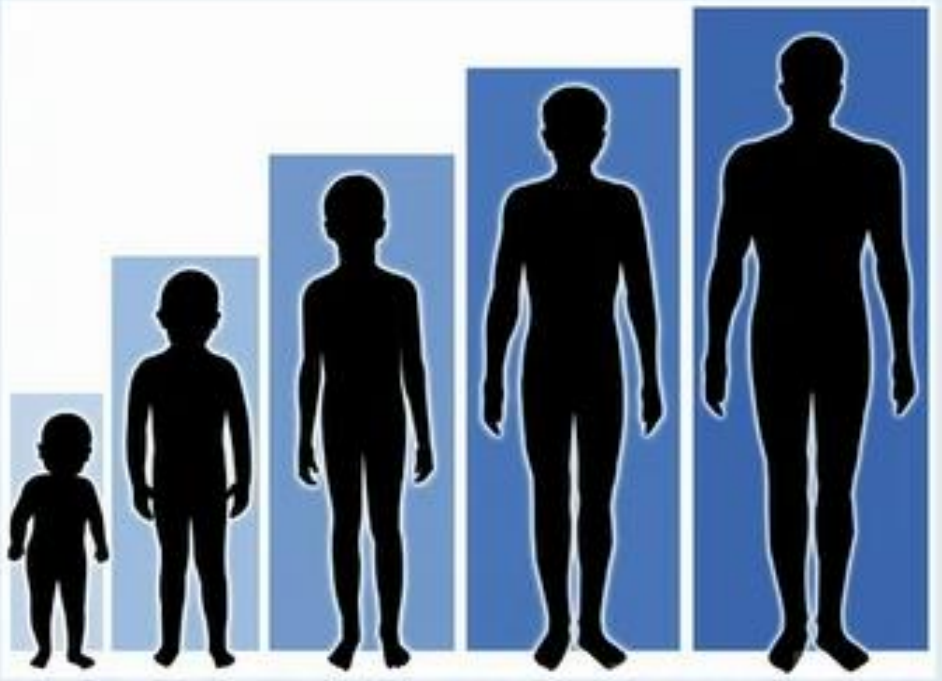
Quotidian Fever

- >39°C often at regular daily intervals
- Can persist, associated with flares

Evanescent Rash

- Typical salmon-pink, macular rash





sJIA before 16Y & AOSD after 16Y

Arthritis

- Arthralgia and myalgia
- Arthritis with potential polyarticular joint involvement
- Risk of erosive destruction and loss of function

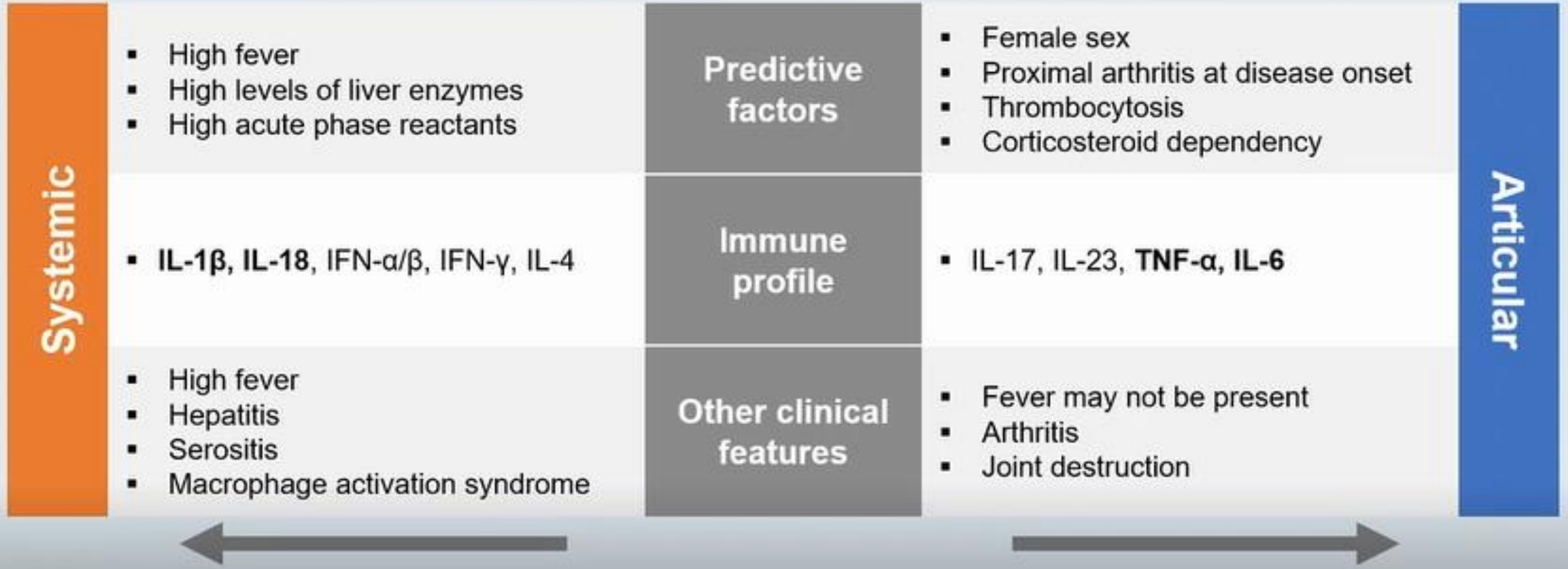
Inflammation

- Elevated neutrophils
- Elevated platelets
- Elevated acute phase response and ferritin
- Elevated S100 proteins[5]

- 1.Ravelli A, Martini A. *Lancet*. 2007;369:767-778; 2. De Benedetti F, Schneider R. Systemic Juvenile Idiopathic Arthritis. In: Cassidy JT, Laxer RM, Petty RE, Lindsley CB, eds. *Textbook of Pediatric Rheumatology*. 6th ed. Philadelphia, PA: Saunders Elsevier; 2011;236-247. 3. Woo P. *Nat Clin Pract Rheumatol*. 2006;2:28-34. 4. Schneider R and Laxer RM. *The Rheumatologist*. May 9, 2012. Available at: https://www.the-rheumatologist.org/article/systemic-juvenile-idiopathic-arthritis/. Accessed September 28, 2020.
5. Wittkowski H et al. *Arthritis Rheum*. 2008;58:3924-3931.

Should think in two dimensions? Systemic and articular AOSD

Disease course of refractory AOSD can be categorised into 2 subsets[1]

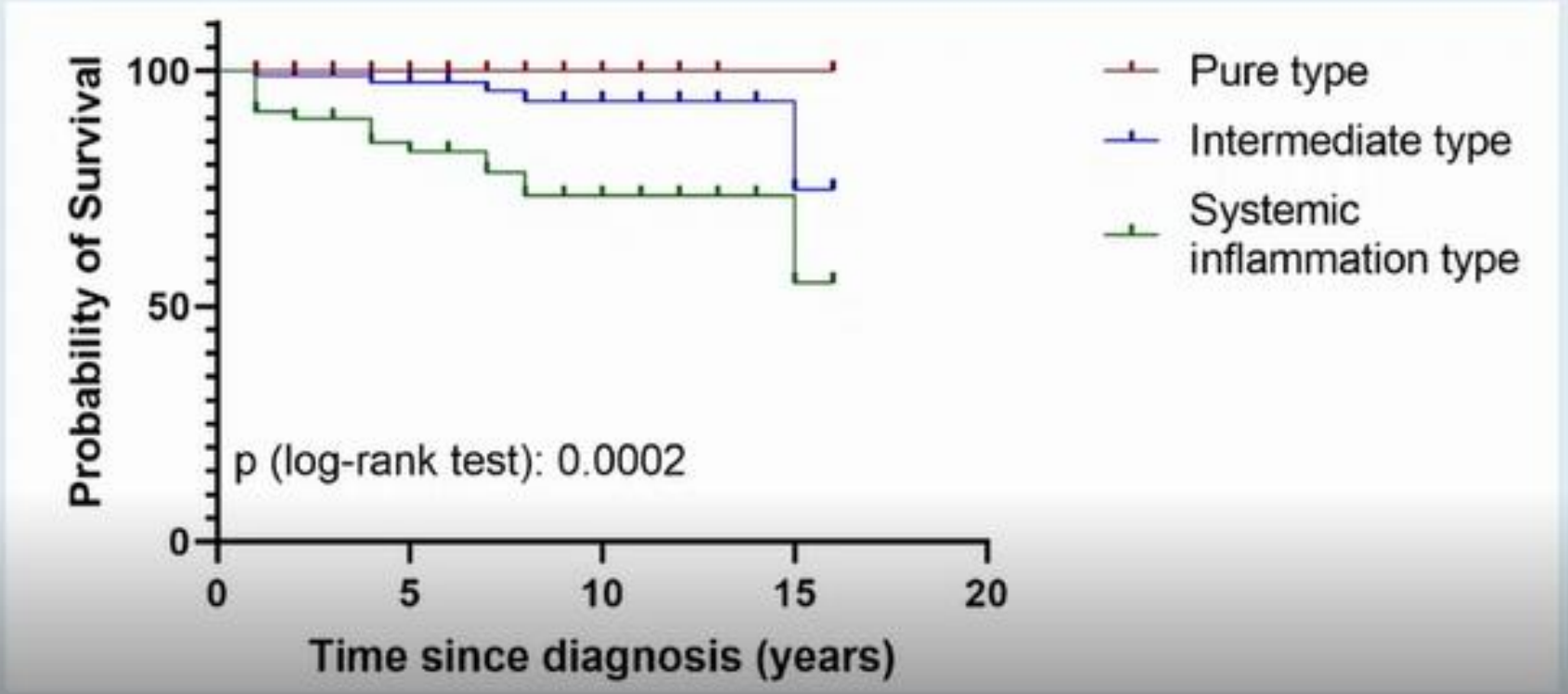


- AOSD, adult-onset Still's disease; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor

- Jamilloux Y, et al. *Ther Clin Risk Manag*. 2014;11:33–43

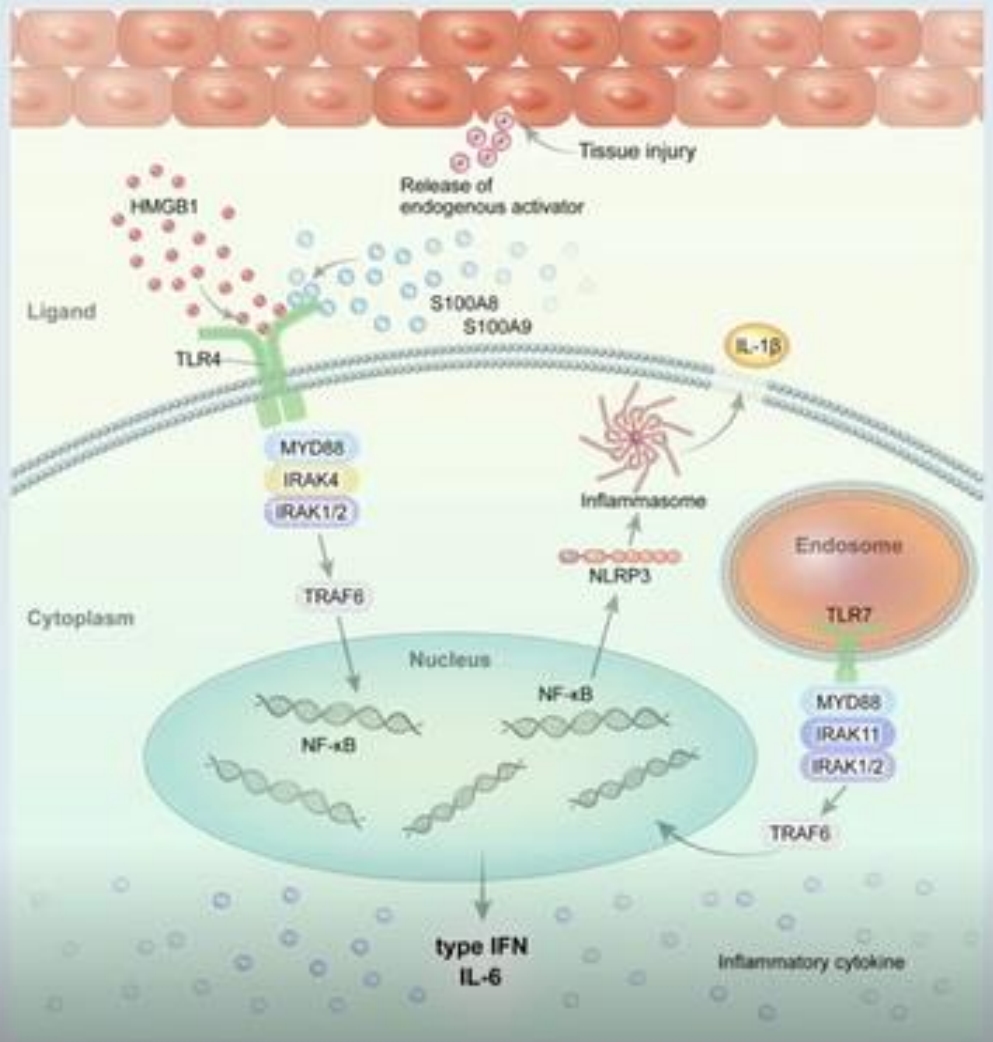
Clinical phenotypes and prognostic factors of AOSD

- Cluster analysis of 492 patients:
- Systemic (34.6%) multiple organ manifestations, highest infection rate and mortality, >50% relapse
- Pure (21.3%) female, rash and joint involvement, no internal organ involvement, mostly monocyclic course
- Intermediate (44.1%) less infection rate, no serious complications



Li R et al., Arthritis Res & Ther 2021

Pathogenesis



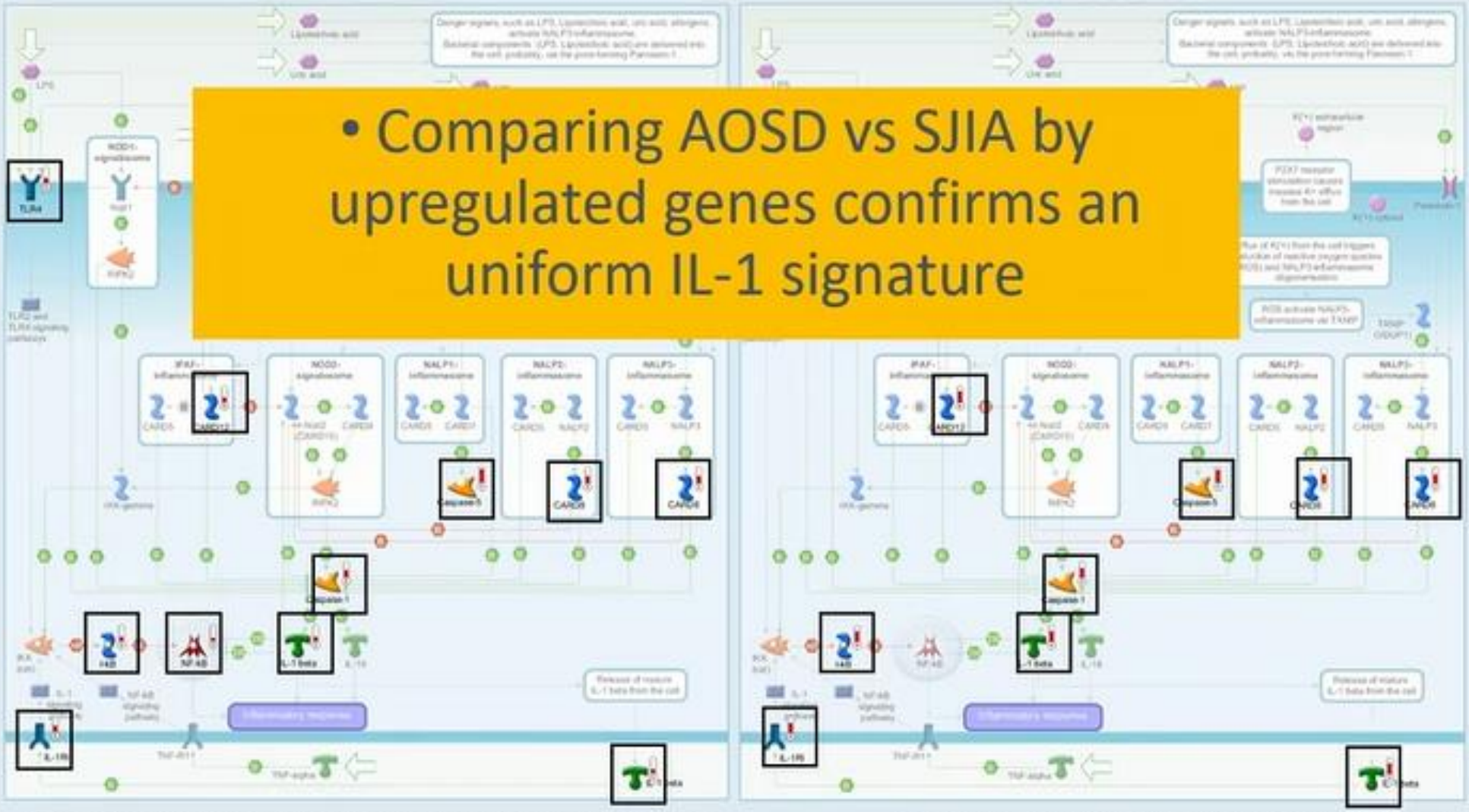
- DAMPs induce the activation of innate immune cells, leading to sterile inflammation
- Endogenous ligands (S100A8, S100A9, and S100A8/A9, and HMGB1) interact with and stimulate the TLR4 pathway
- Activated TLR4 and TLR7 induce NLRP3 inflammasome activation and the secretion of IL-1ß

Jung JY et al., Front Immunol 2020

Cytokine Balance is the Key to Life!

AOSD-vs-HV

SJIA-vs-HV



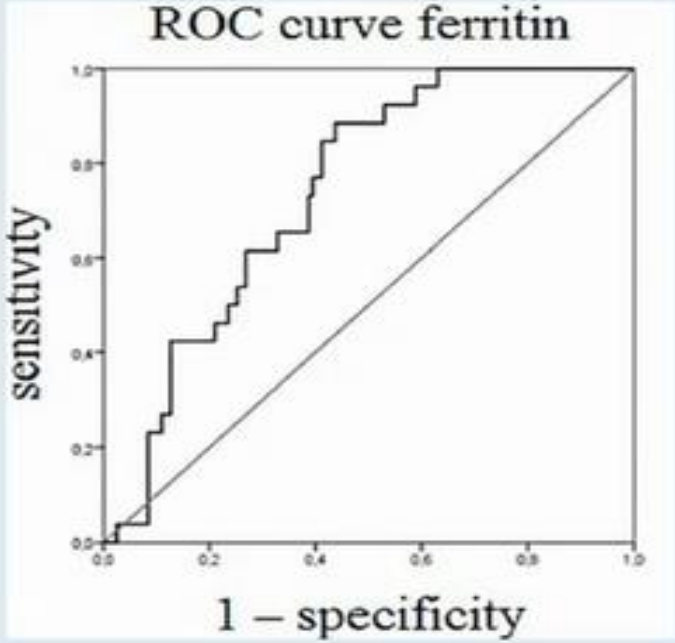
- Comparing AOSD vs SJIA by upregulated genes confirms an uniform IL-1 signature

Black rectangles around the Upregulated genes

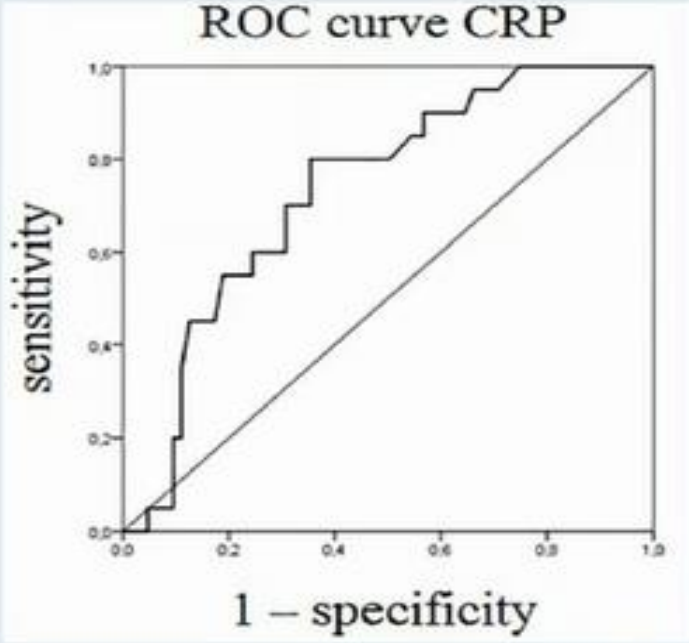
Nirmala et al., Pediatr Rheumatol Online J. 2015

BIOMARKERS

Ferritin and CRP are predictive biomarkers of mortality and macrophage activation syndrome in AOSD



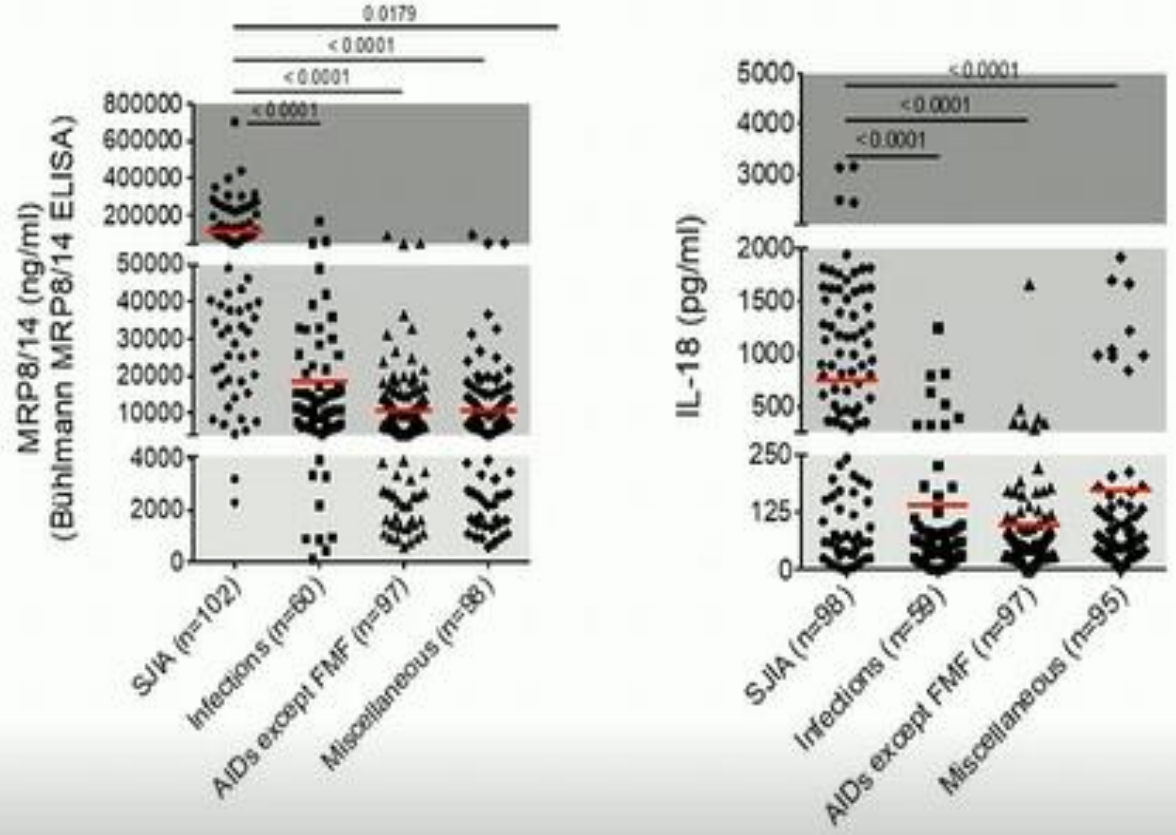
Best cut-off for ferritin was 1225 ng/ml in predicting MAS, providing a sensitivity of 88% and a specificity of 57%.

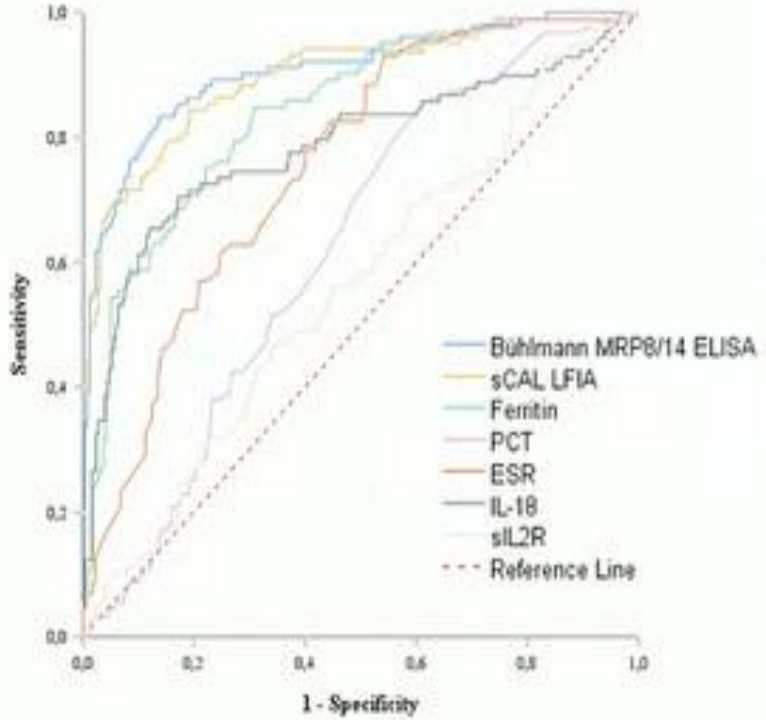


Best cut-off for CRP in predicting mortality was 68.7 mg/L, providing a sensitivity of 80% and a specificity of 65%

Di Benedetto et al., PLOS ONE 2020

- 357 patients with fever of unknown origin
- Retrospectively confirmed diagnosis (after 1 year)
- Validation of S100, other biomarkers





MRP8/14 or IL-18 elevated

80/88 patients correctly positive
(Sensitivity 92%)

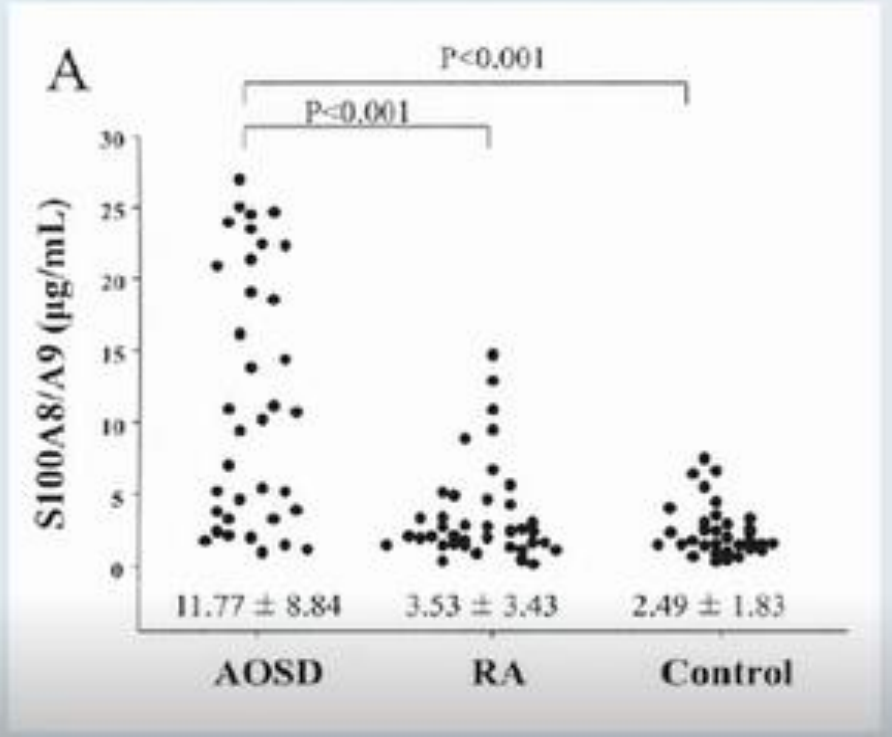
MRP8/14 and IL-18 low

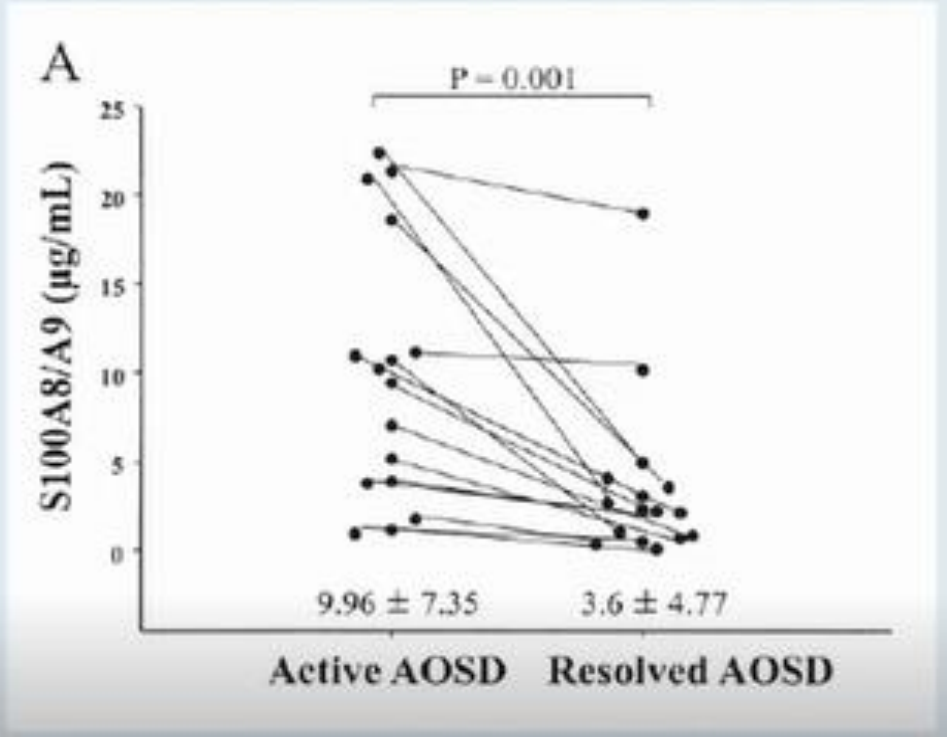
208/214 patients correctly negative
(Specifity 97%)

Park C et al. Rheumatology 2021

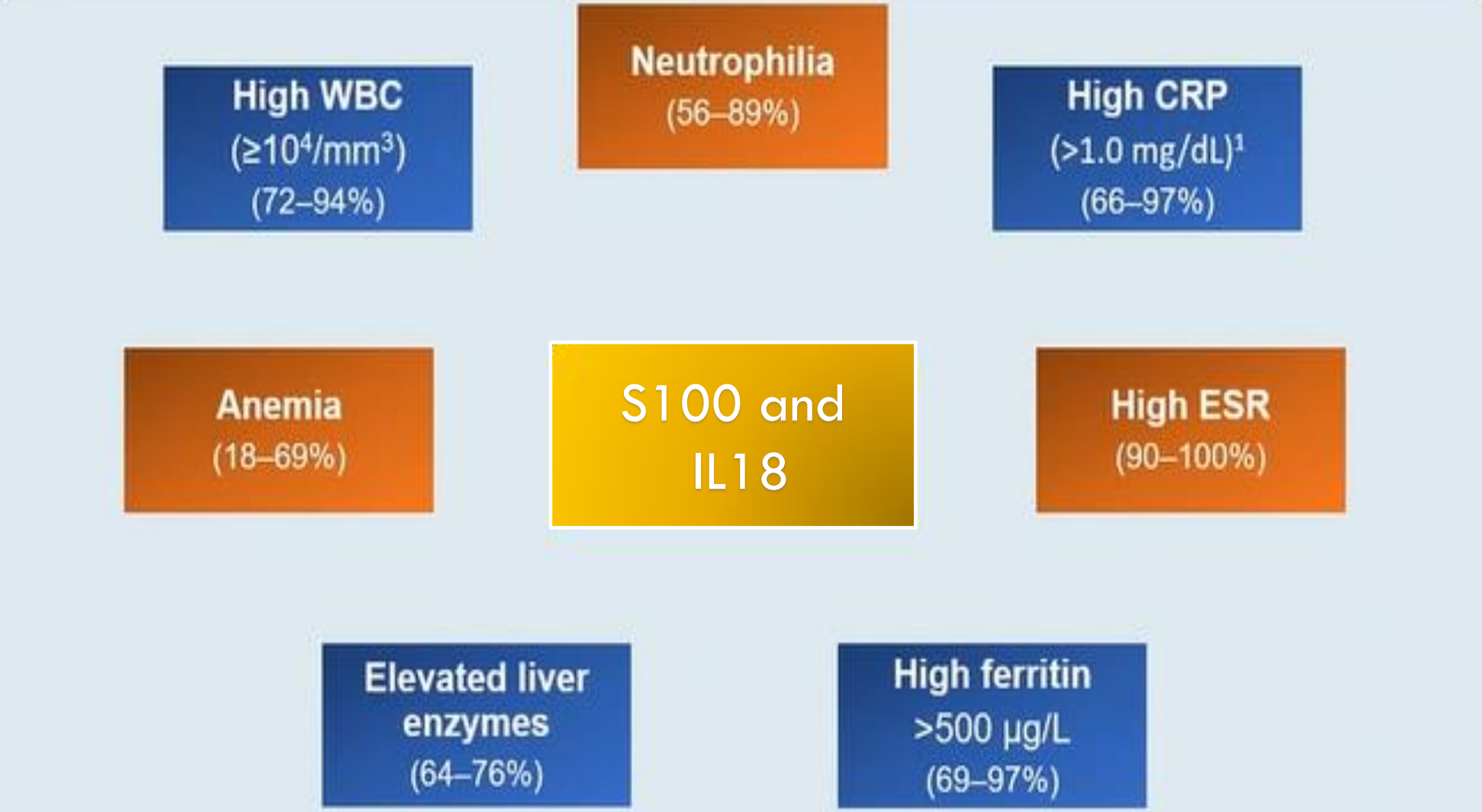
S100 Proteins as Biomarkers for AOSD

- Serum levels of S100A8/A9 are significantly elevated and correlate with disease activity





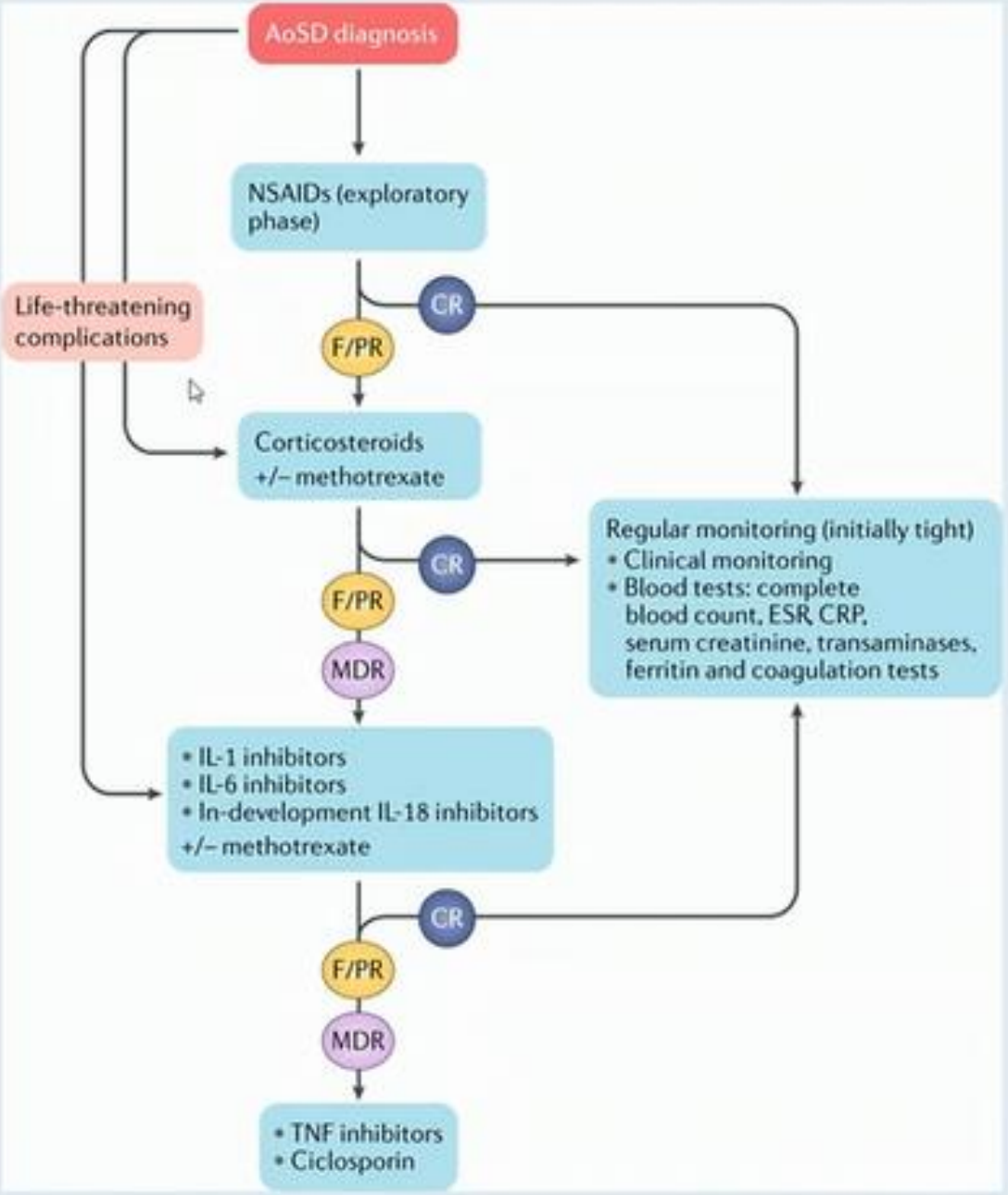
Kim HA et al. J Rheumatol 2012



- Laboratory features suggest significant systemic inflammation

- Gerfaud-Valentin M, et al. *Autoimmun Rev* 2014;13:708–22. 1. Chen D-Y, et al. *J Rheumatol* 2004;31:2189–98.

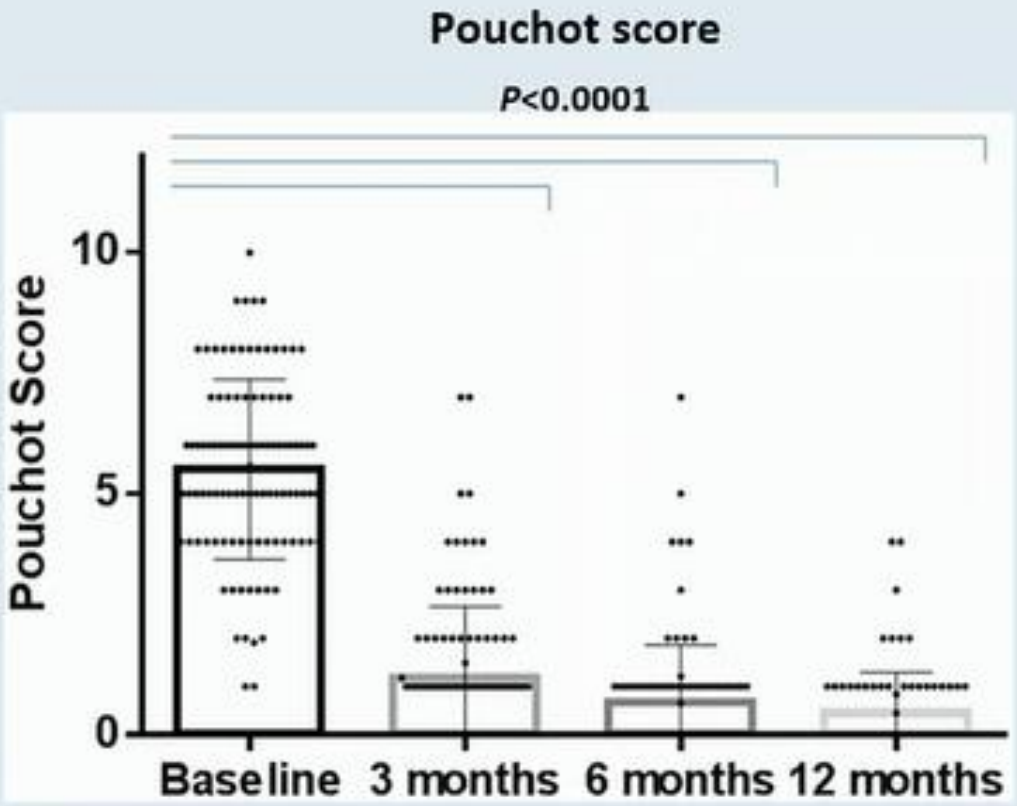
How to improve therapeutic strategies?

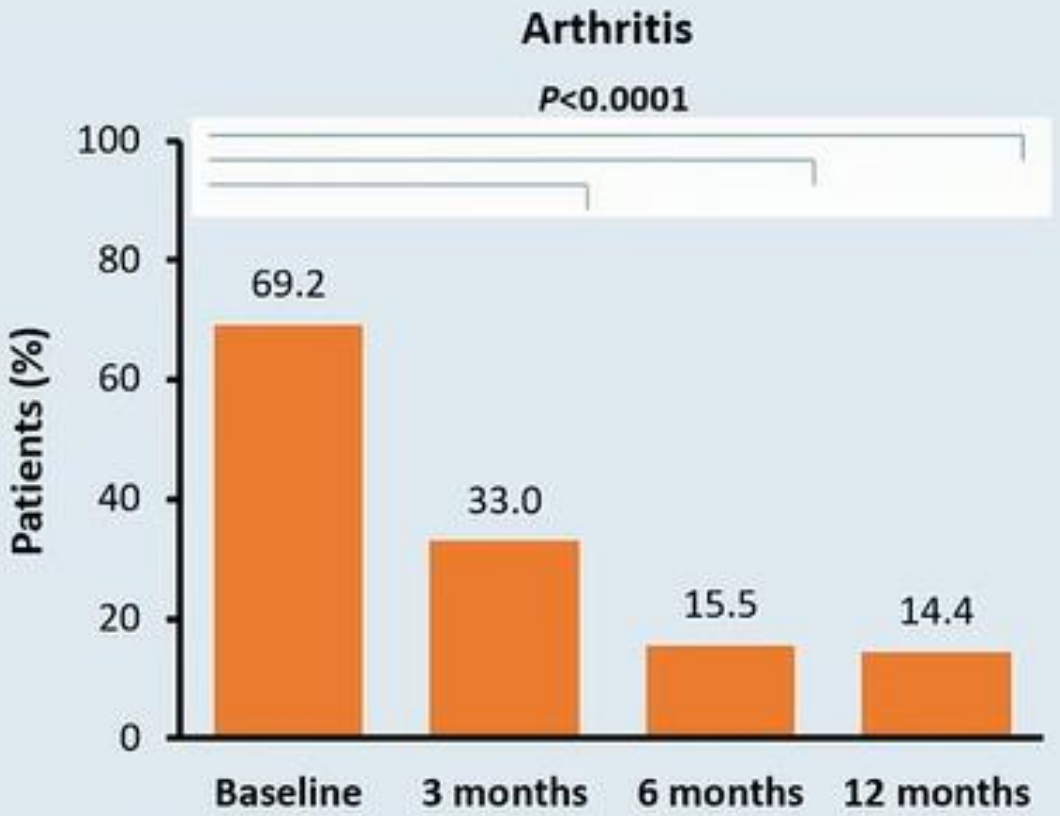


AOSD, adult-onset Still's disease; CR, complete remission; CRP, C-reactive protein; F, failure; IL, interleukin; MDR, multidisciplinary round; NSAID, nonsteroidal anti-inflammatory drug; PR, partial remission; TNF, tumor necrosis factor

Feist, E, et al. *Nat Rev Rheumatol* 2018;14:603-6

IL-1 inhibition significantly improved clinical and serological manifestations of AOSD

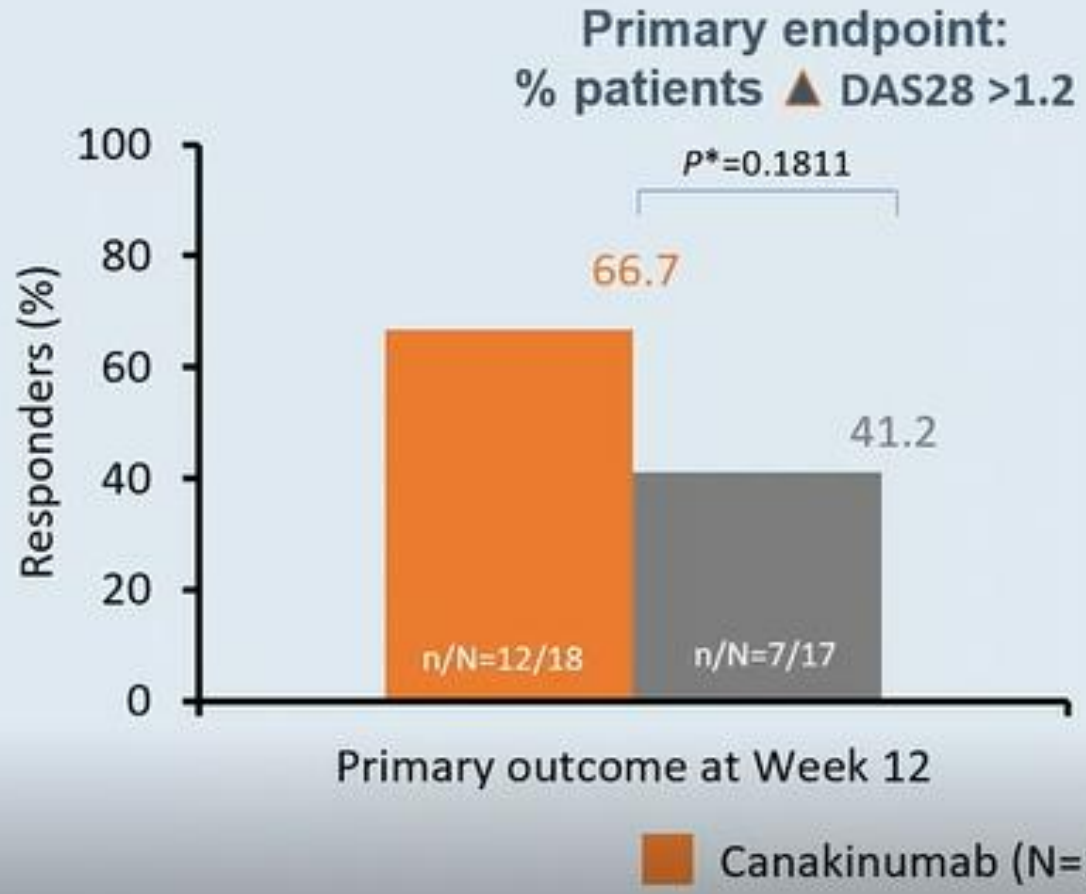


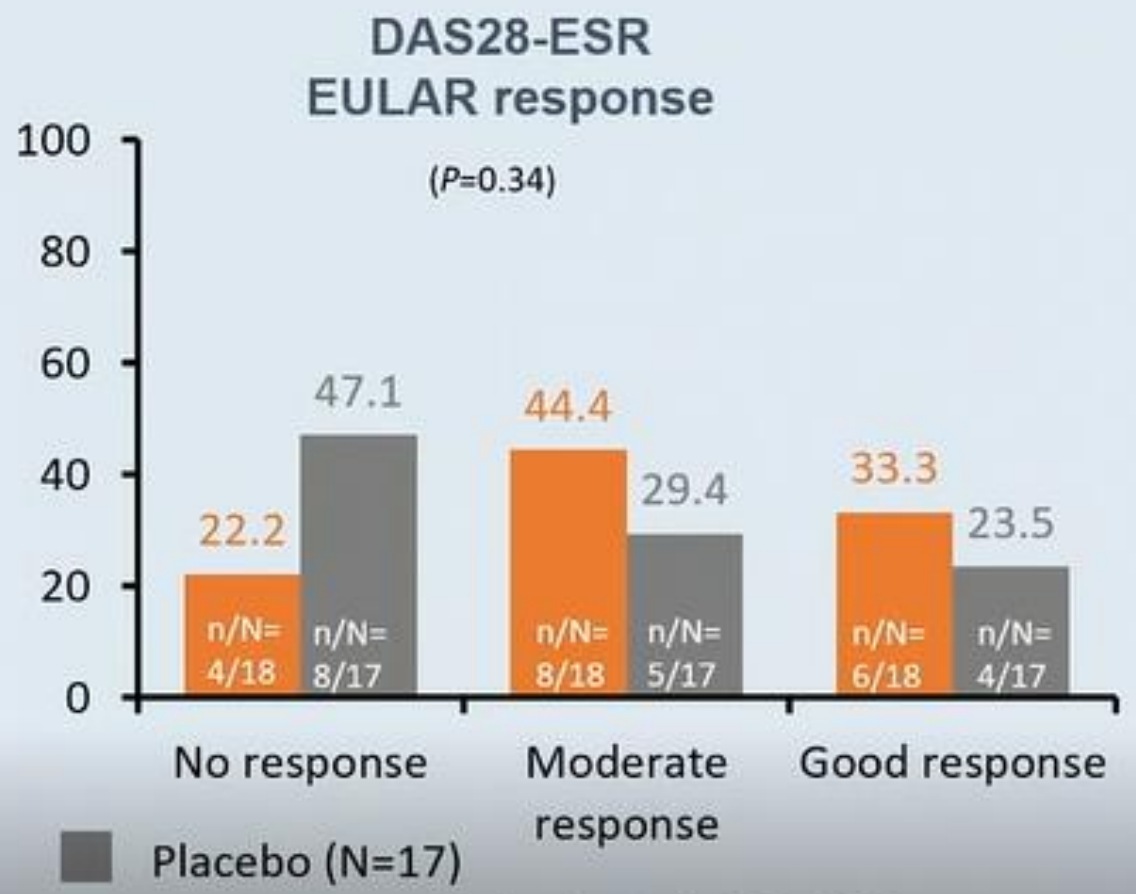


- Multicenter, retrospective, observational study in 140 Italian patients with adult-onset Still's disease. 40 patients were treated with anakinra; 4 were subsequently switched to canakinumab following anakinra failure. Data shown for anakinra-treated patients
  Pouchot score captures changes in fever, rash, pneumonia, pericarditis, pleuritis, sore throat, lymphadenopathy, hepatomegaly, myalgia, arthritis, macrophage activation syndrome

- Colafrancesco S, et al. *Front Pharmacol*. 2017;8:369

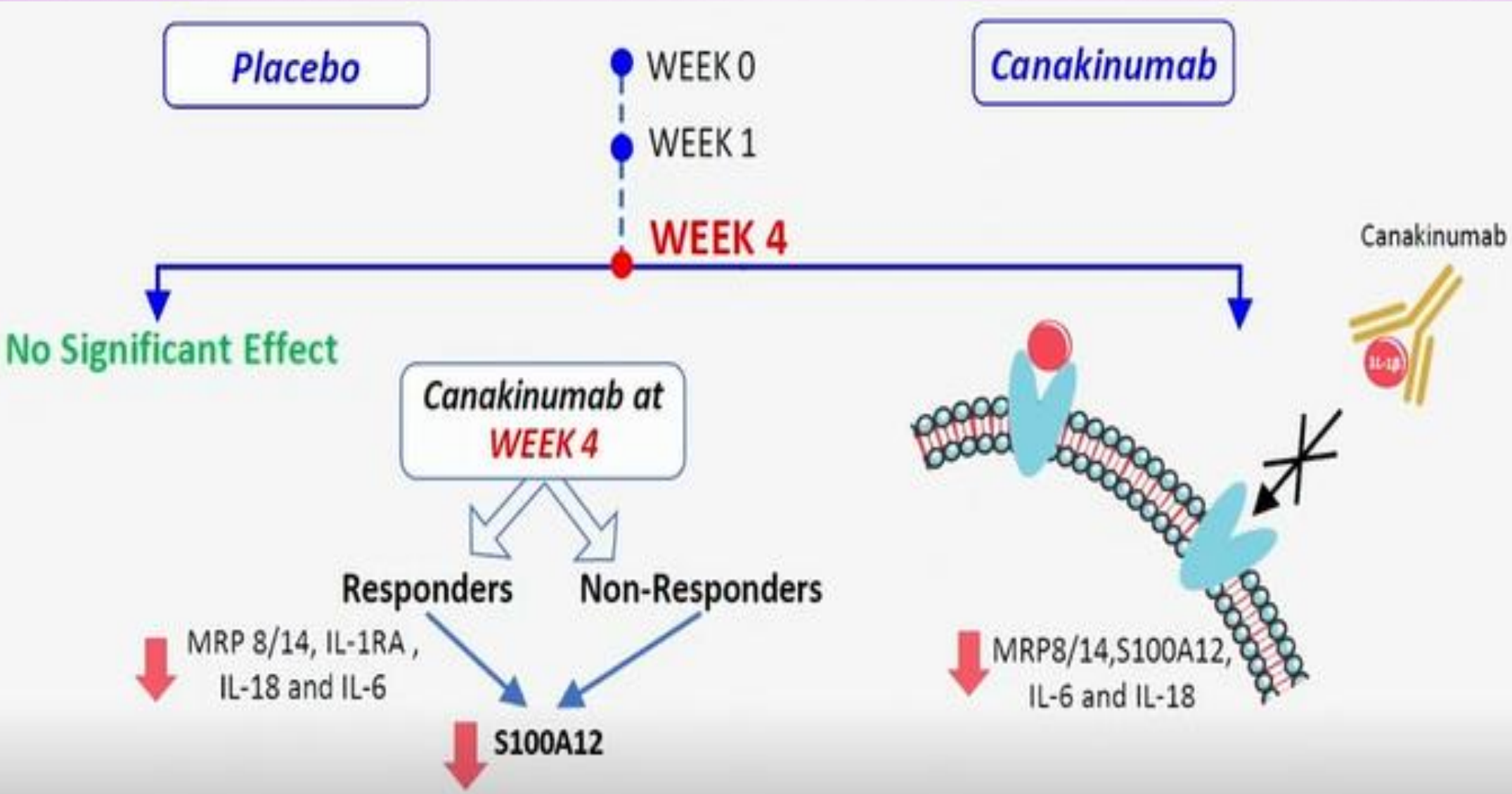
More patients had clinically-meaningful improvements in disease activity with Canakinumab vs placebo at Week 12 (ITT)





- *Fisher's exact test
n, number of responders; N, total number of patients; DAS28, 28-joint disease activity score; ITT, intent to treat

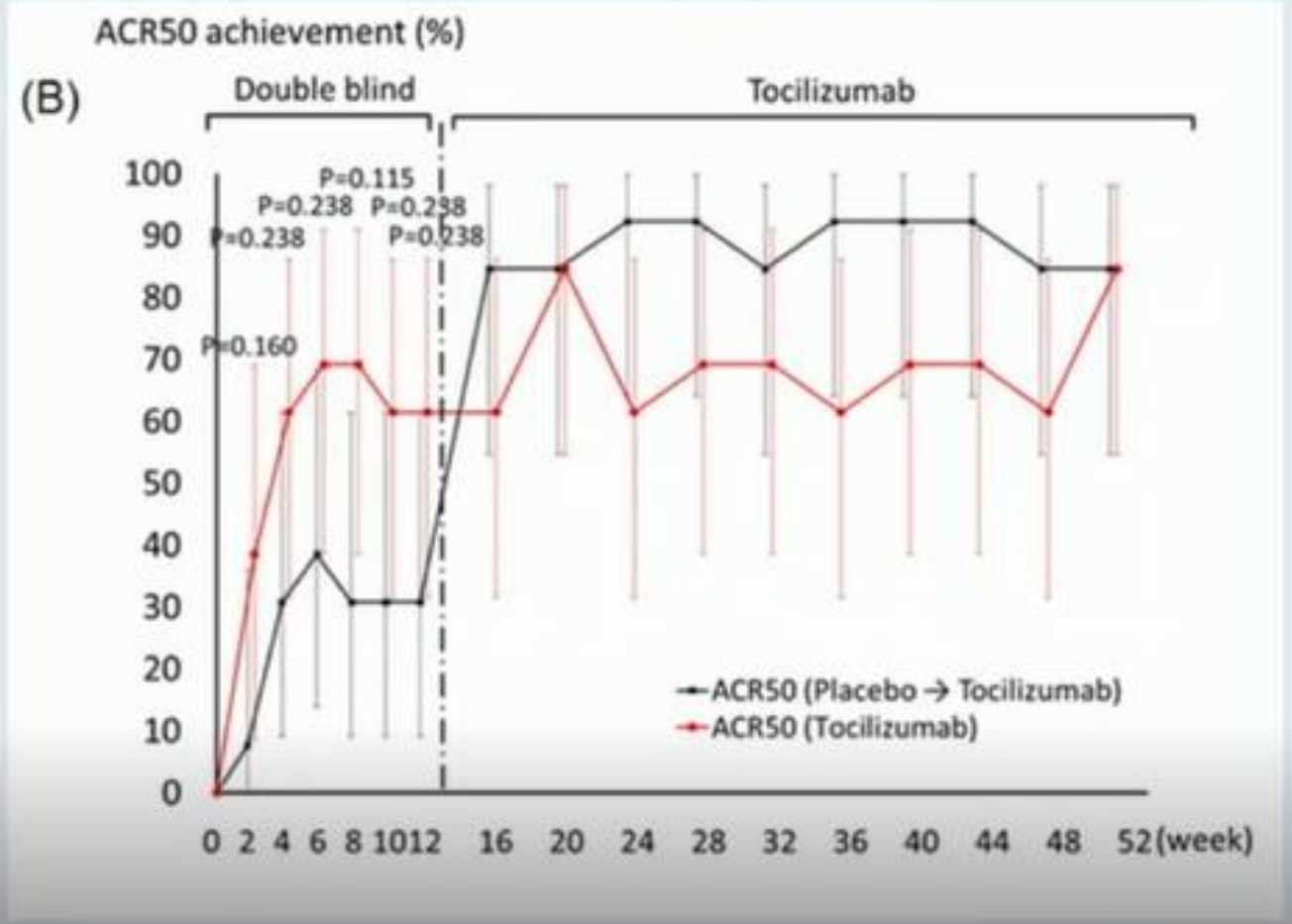
- Kedor C, et al. ARD 2020, doi:10.1136/annrheumdis-2020-21715



- Ghannam K et al., J Clin Med 2021

Tocilizumab in patients with AOSD refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial

- 27 patients with AOSD refractory to GC were randomised to tocilizumab at a dose of 8 mg/kg or placebo given IV every 2 weeks during the 12-week, double-blind phase.
- Patients received open-label tocilizumab for 40 weeks subsequently



- Kaneko Y et al, ARD 2018

Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany

Claas H. Hinze[1*], Dirk Holzinger[1,2], Elke Lainka[3], Johannes-Peter Haas[4], Fabian Speth[4], Tilmann Kallinich[5],

Consensus Treatment Plans

Option 1:
Glucocorticoids
Prednisolone
(1-2 mg/kg/d; max. 80 mg/d)
+/-
Methylprednisolone i.v. 3 days
(20-30 mg/kg/d; max. 1 g/d)

Option 2:
Anakinra
(2-4 mg/kg/d; initially max. 100 mg)
+/-
Glucocorticoids (as in option 1)

Option 3:
Canakinumab
(4 mg/kg; max. 300 mg; q 4 wks)
+/-
Glucocorticoids (as in option 1)

Option 4:
Tocilizumab
(≥30kg: 8 ml/kg q 2 wks, max. 800 mg
<30kg: 12 mg/kg q 2 wks)
+/-
Glucocorticoids (as in option 1)

May be added:

Intraarticular GCs, NSAR, MTX

Control after 7 days: Target 1 achieved?
- No fever
- CRP reduced by at least 50 %

✓ → **Dose reduction Glucocorticoids** and/or **Keep on Biologic**

✗ → **Start or increase dose Glucocorticoids** and/or **Start or increase dose Biologic** or **Switch Biologic**

Control after 4 weeks: Target 2 achieved?
- MD global assessment reduced by ta least 50 % **and**
- Active joint countreduced by at least 50 % **or**
- JADAS-10 Score max. 5,4

✓ → **Stop Glucocorticoids** and/or **Reduce** or **Stop Biologic**

✗ → **Increase dose Biologic** or **Switch Biologic**

Control after 6-12 months : Target 3 achieved?
- Clinically inactive disease without GCs

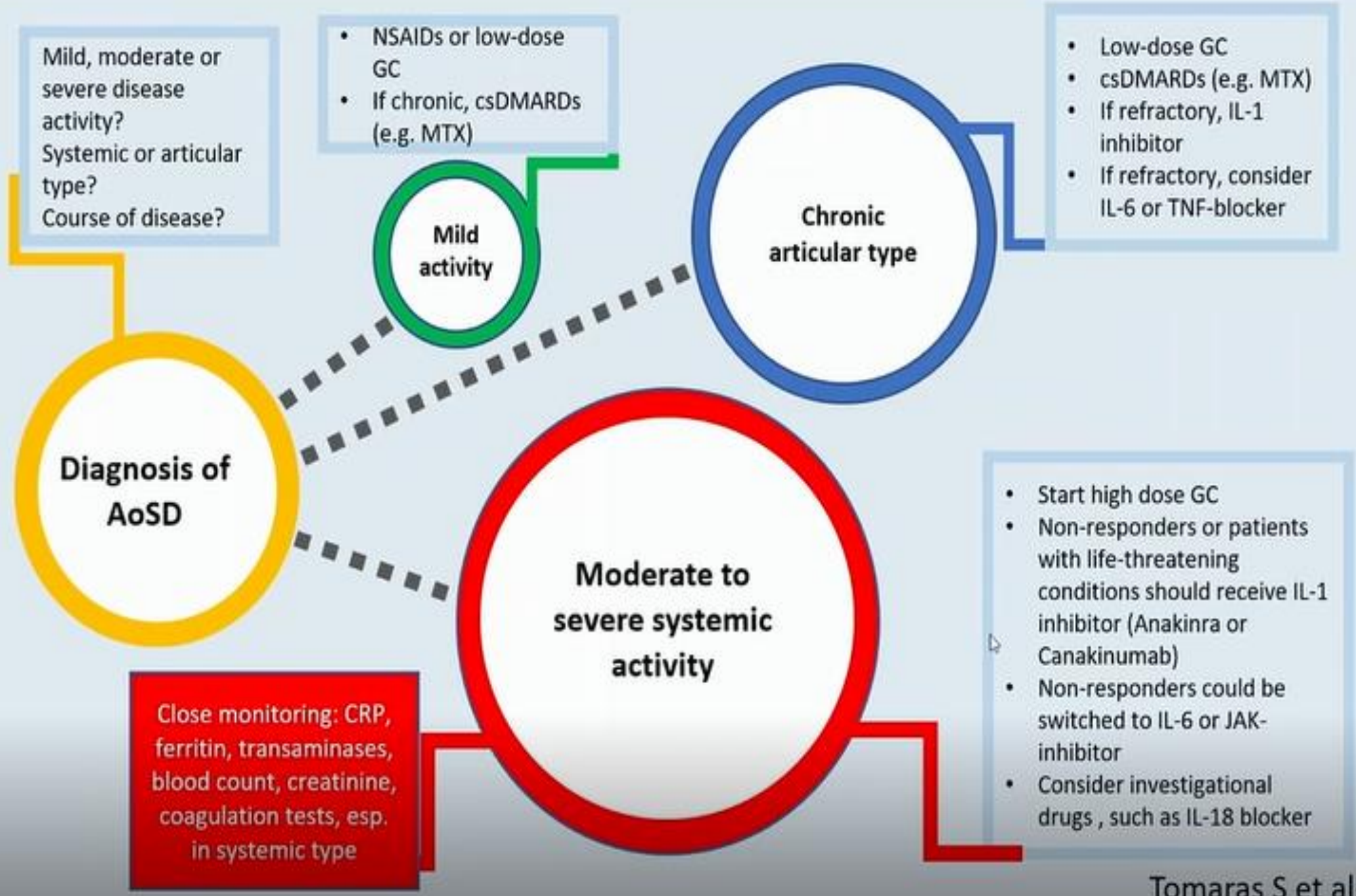
✗ → **If polyarthritis without systemic manifestations** consider **TNF-Inhibitor** or **Abatacept**

Control after ≥ 1 year: Target 4 achieved?
- Clinical remission

✓ → **Stop antirheumatic therapy if remission is maintained**

✗ → **Discuss alternative therapies**

Hinze C et al. Pediatr Rheumatol Online J 2018;16:7



Tomaras S et al., JCM 2021

IN SUMMARY

- STARTING THERAPY EARLY IS CRUCIAL :EARLY DIAGNOSIS WITH THE USE OF BIOMARKERS AND BETTER DIAGNOSTIC CRITERIA IS THE KEY TO SUCCESS
- DEVELOPPMENT OF NEW OUTCOMES MEASURES AND TREATMENT GUIDELINES IS NEEDED URGENTLY
- DEVELOPPMENT AND VALIDATION OF A EULAR DISEASE ACTIVITY SCORE FOR AOSD