
بسم الله الرحمن الرحيم

ROLE OF TOCILIZUMAB FOR THE TREATMENT OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

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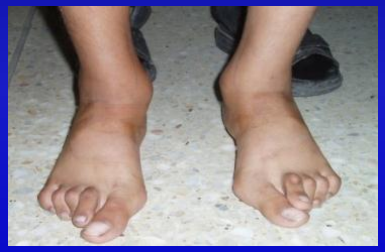
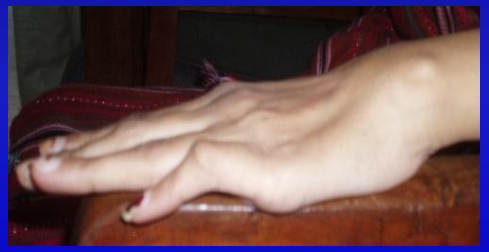
Juvenile Idiopathic Arthritis

JIA is the most common rheumatic diseases of childhood & a major cause of short & long term disability





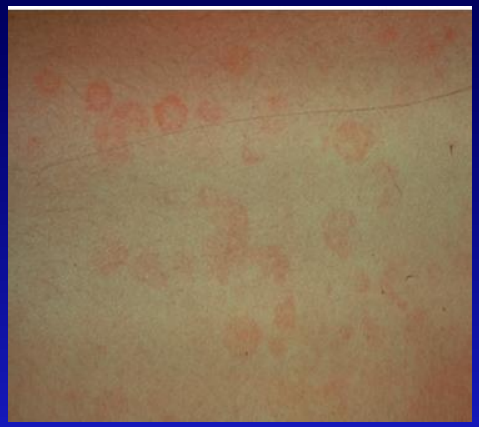
ILAR Classification

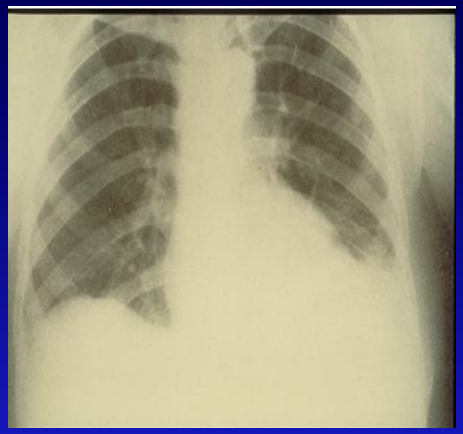
JIA is an arthritis of unknown cause, beginning before age 16 yr & lasting for at least 6 weeks.

- **Systemic onset JIA**
- Oligo-arthritis
  - Persistent
  - Extended
- Polyarthritis (RF -ve)
- Polyarthritis (RF +ve)
- Psoriatic arthritis
- Enthesitis related arthritis
- Undifferentiated arthritis

•From Firestein GS, Budd RC, Harris ED Jr, et al, editors: Kelleys textbook of rheumatology, ed 8, Philadelphia, 2009, Saunders/Elsevier

SYSTEMIC ONSET JIA

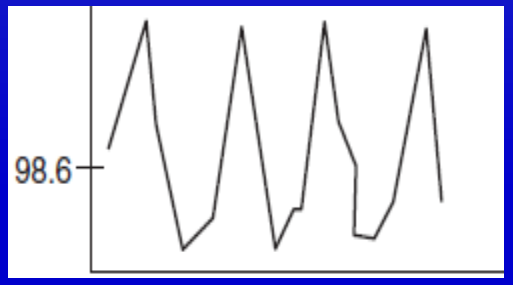




Systemic onset JIA

Arthritis in one or more joints with / preceded by fever of at least 2 weeks duration that is documented to be daily (“quotidian”) for at least 3 days & accompanied by one or more of the following:

- Evanescent (non-fixed) erythematous rash
- Generalized lymph node enlargement
- Hepatomegaly and/or splenomegaly
- Serositis



Pathophysiology of SOJIA

- Abnormal expression of pro-inflammatory cytokines…IL-6, IL-1, IL-18, TNF-α
- IL-6
  - consistent with high spikes of fever, thrombocytosis, microcytic hypochromic anaemia, growth retardation
  - induces an increase in concentration of IL-1 receptor antagonist
- anti-inflam cytokine… IL-10 response is deficient
- Auto-antibodies & immune complex form rare

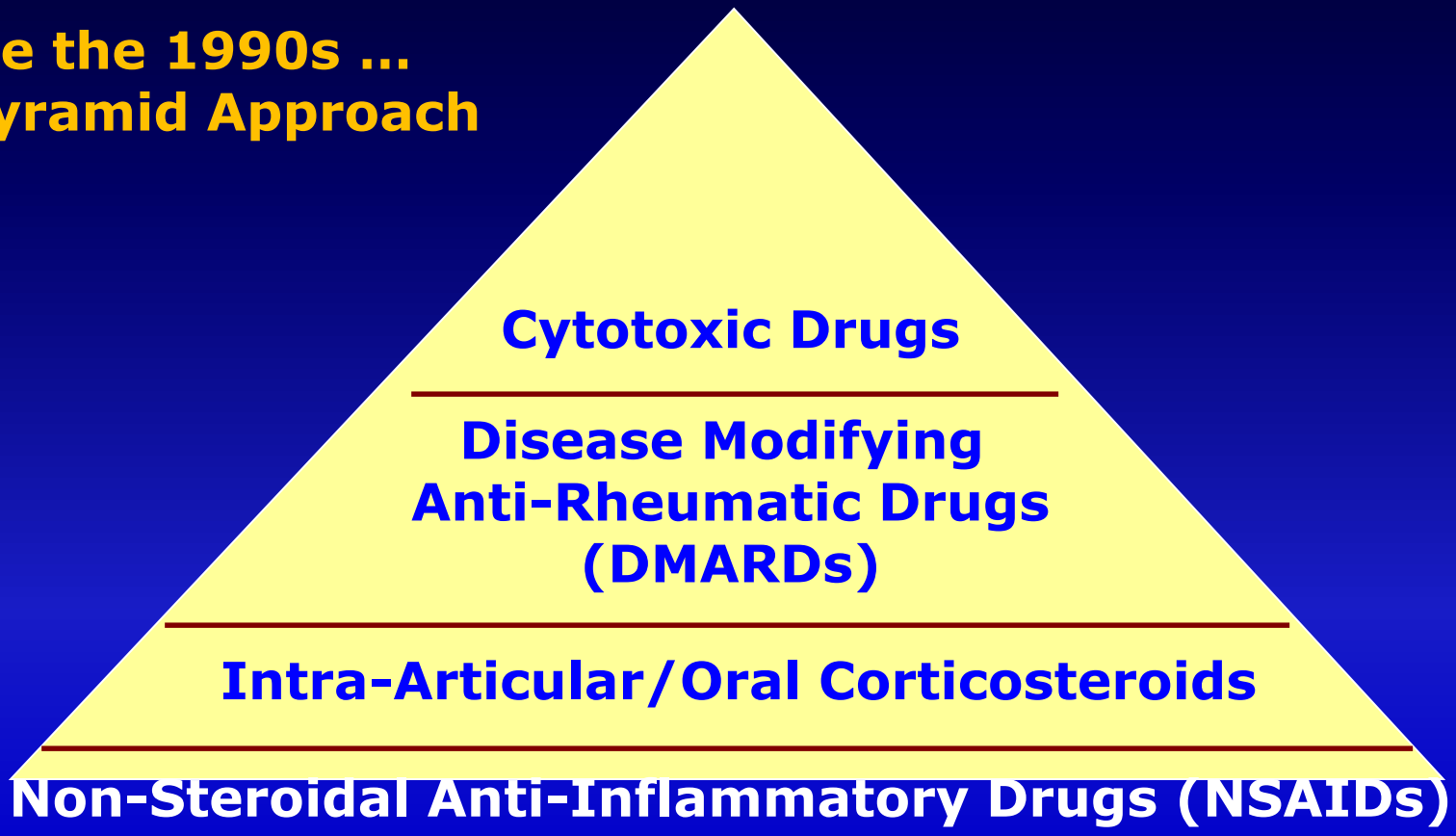
MANANGEMENT

Objectives of Treatment

- Immediate
  - Relieve discomfort
  - Preserve function
  - Prevent deformities
- Long term
  - Minimize the effects of disease & treatment
  - Promote normal growth and development
  - Rehabilitation
  - Education of patient & parent

Traditional approach for the Treatment of JRA

Before the 1990s …
Pyramid Approach



Evolving Treatment of JIA

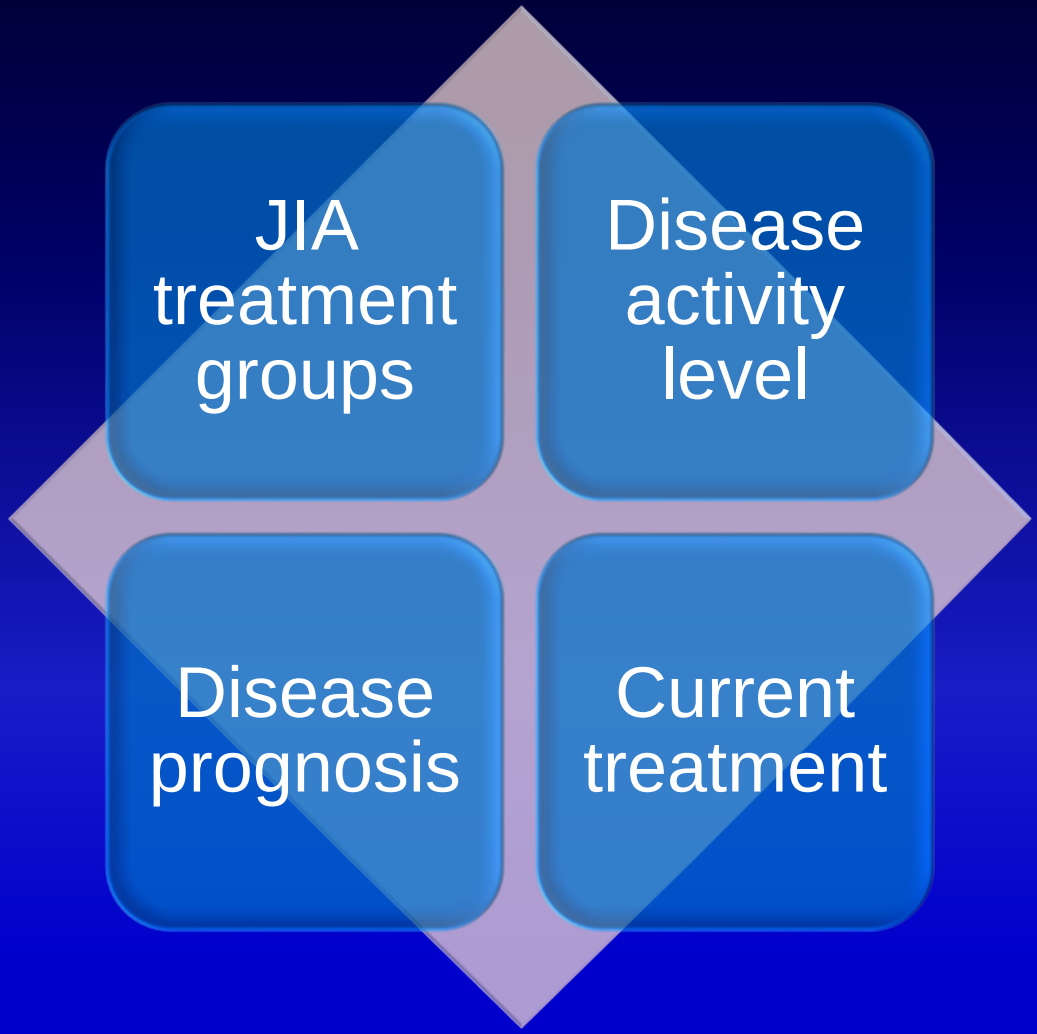
Since the 1990s and into the 2000s…

Paradigm shift….

The trend in managing JRA is much more aggressive treatment earlier in the disease course with the goal of preventing joint damage and slowing progressive articular damage.

2011 AMERICAN COLLEGE OF RHEUMATOLOGY RECOMMENDATIONS FOR THE TREATMENT OF JIA

2011 ACR Recommendations for the Treatment of JIA



JIA Treatment Groups

- H/O ≤ 4 joints involved
- H/O ≥ 5 joints involved
- Active Sacroiliac arthritis
- Systemic arthritis with active Systemic symptoms
- Systemic arthritis with active arthritis

Disease Activity Level

- Active joint count
- ESR / CRP
- Physician global assessment of overall disease activity score
- Patient / Parent global assessment of overall wellbeing score
- Categorized as……Low, Moderate, High

Disease Prognosis

- Features of poor prognosis…present, absent
- Different acc to JIA Treatment type
- Systemic arthritis
  - Fever of 6 month's duration
  - Elevated inflammatory markers
  - GC therapy > 6months
  - Radiographic changes
  - Hip joint arthritis

Drugs

- NSAIDS
- Corticosteroids
  - Oral, I/V, Intra-articular
- Non-Biologic DMARD's
  - Methotrexate
  - sulphasalazine
- Biologic DMARD's
  - TNF-α inhibitors….Etanercept / Abatacept
  - IL-1 receptor antagonist….Anakinra

?? TOCILIZUMAB ??
(anti-IL-6)

ACR determined ….treatment of SOJIA should be the focus of the first update

Why and What?

- Better understanding of patho-physiology of SOJIA
- Rapid increase in data reg. treatment of SOJIA
- SOJIA differs from other categories of JIA & is the severest type of JIA
- Growth retardation & steroid side effects are common
- Low efficacy of methotrexate to SOJIA

Why and What?

- Course ….monocyclic course (lasts 2 to 4 years), relapsing course, chronic progressive course
- MAS (life-threatening condition) is more common
- mortality rate…hospitalized with SOJIA & MAS is estimated to be as high as 6% or higher

2013 update of the 2011 ACR recommendations for the treatment of juvenile idiopathic arthritis

Sarah Ringold, Pamela F. Weiss, Timothy Beukelman, Esi Morgan DeWitt,
Norman T. Ilowite, Yukiko Kimura, Ronald M. Laxer, Daniel J. Lovell,
Peter A. Nigrovic, Angela Byun Robinson, Richard K. Vehe
ARTHRITIS & RHEUMATISM
Vol. 65, No. 10, October 2013, pp 2499–2512

Aims of the project

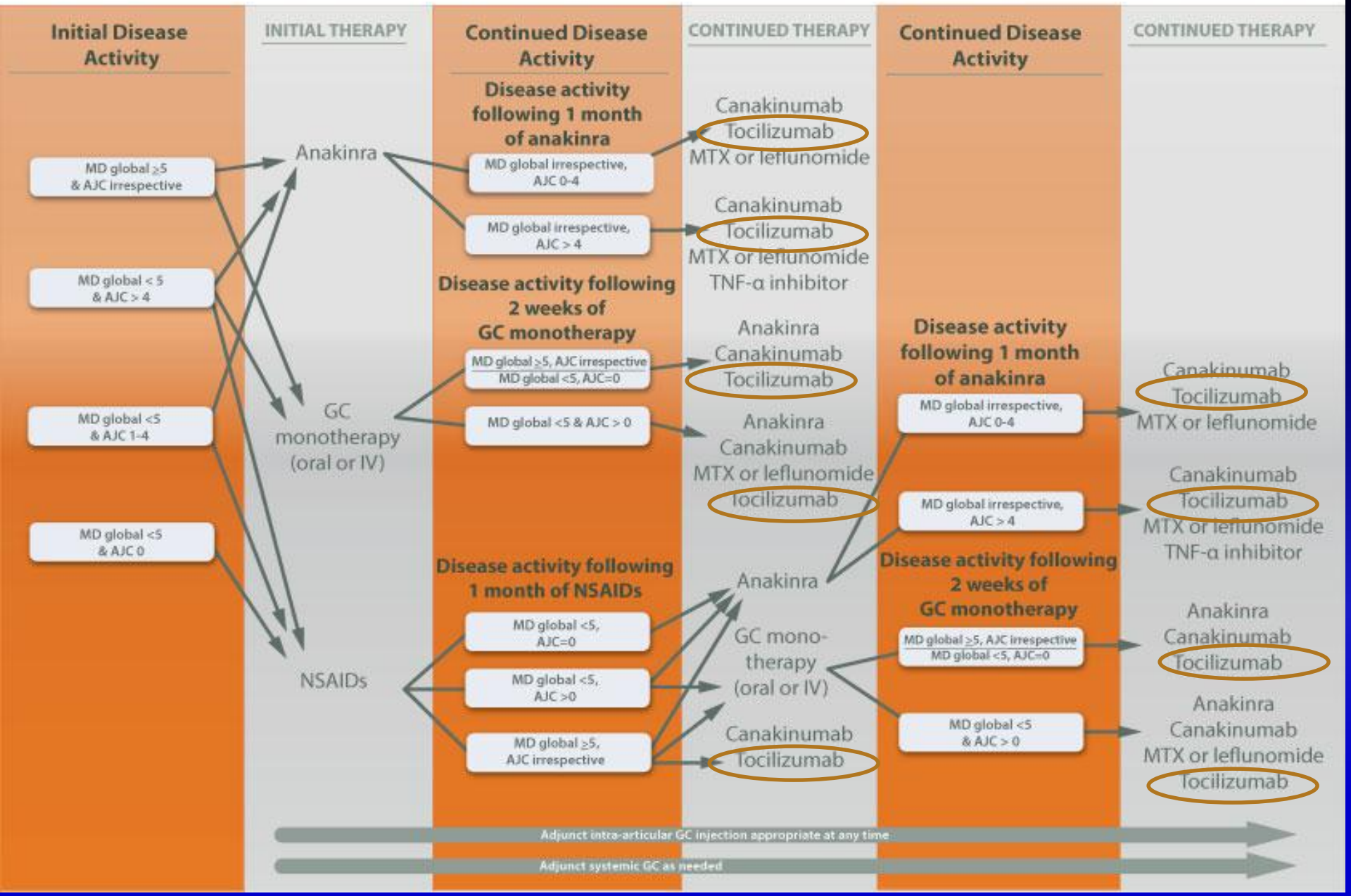
- Incorporate the use of anti–IL-1 & anti–IL-6 therapies into ACR recommendations for SOJIA
- Develop treatment recommendations for patients with 3 general SOJIA phenotypes:
  - sig systemic features & varying degrees of synovitis
  - sig arthritis & no sig systemic features
  - features concerning for MAS

Biologics in SOJIA

Table 1. Medications evaluated for the treatment of systemic juvenile idiopathic arthritis*

	2011 recommendations	2013 recommendations
NSAIDs†	X	X
Glucocorticoids	X	X
Methotrexate	X	X
Leflunomide	X	X
IVIG	X	X
Calcineurin inhibitors‡	X	X
TNFα inhibitors§	X	X
Abatacept	X	X
Rituximab	X	X
Anakinra	X	X
Canakinumab		X
Rilonacept		X
Tocilizumab		X

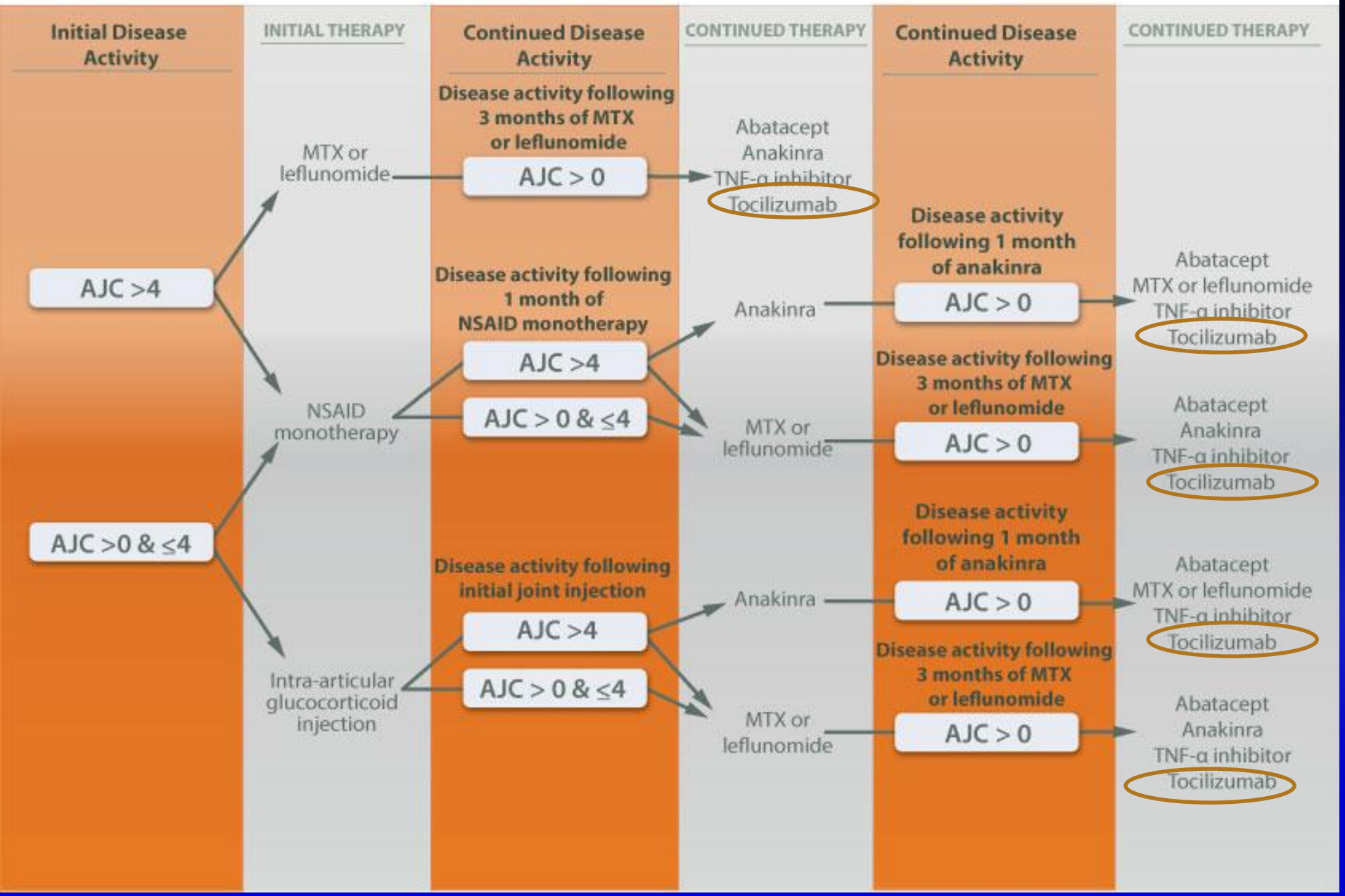
PATIENT WITH ACTIVE SYSTEMIC FEATURES & VARYING DEGREES OF SYNOVITIS



Patients with Active Systemic Features & varying degree of Synovitis

- Tocilizumab.. for continued disease activity
  - following GC monotherapy, MTX or leflunomide or anakinra irrespective of the MD global and AJC
  - in patients with MD global ≥ 5 ,irrespective of AJC despite prior NSAID monotherapy
- Not for continued disease activity
  - IVIG, MTX or leflunomide, rilonacept, rituximab inappropriate, until anakinra or tocilizumab tried

PATIENT WITHOUT ACTIVE SYSTEMIC FEATURES & VARYING DEGREES OF SYNOVITIS



Patients without Active Systemic Features & varying degree of Synovitis

- Tocilizumab.. for continued disease activity following treatment with anakinra , MTX or leflunomide with AJC >0, irrespective of MD global
- Abatacept, TNF-α inhibitor & rituximab indicated after anakinra & Tocilizumab tried

Tocilizumab ….IL-6 blocker is treatment of choice in SOJIA patients with continued disease activity

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

Yokota S[1], Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, Iwata N, Umebayashi H, Murata T, Miyoshi M, Tomiita M, Nishimoto N, Kishimoto T

Lancet.

2008 Mar 22;371(9617):998-1006.

Tocilizumab for the Treatment 0f Systemic Juvenile Idiopathic Arthritis

NICE technology appraisal guidance 238

guidance.Nice.org.Uk/ta238

issued: December 2011

Retrospective analysis of efficacy and safety of tocilizumab treatment in patients with severe systemic-onset juvenile idiopathic arthritis followed for 12 months

E. I. Alexeeva,1,2 A. A. Baranov,1,2 R. V. Denisova,1 S. I. Valieva,1 T. M. Bzarova,1 K. B. Isaeva,1 T. V. Sleptsova,1 E. V. Mitenko,1 N. I. Taybulatov,1 E. G. Chistyakova,1,2 and A. N. Fetisova1

ISRN Immunology

Volume 2013 (2013), Article ID 548312

Successful treatment with tocilizumab every 4 weeks of a low disease activity group who achieve a drug-free remission in patients with systemic-onset juvenile idiopathic arthritis

Mikhail M Kostik*, Margarita F Dubko, Vera V Masalova, Ludmila S Snegireva, Tatyana L Kornishina, Irina A Chikova, Eugenia A Isupova, Ekaterina M Kuchinskaya, Natalia I Glebova, Natalia V Buchinskaya, Olga V Kalashnikova and Vyacheslav G Chasnyk

Pediatric Rheumatology 2015, 13:4

Tocilizumab

Tocilizumab (Actemra)

- It is a humanised monoclonal antibody that inhibits the cytokine IL-6
- Reducing the activity of IL-6 can reduce
  - Fever, inflammation in the joints
  - prevent long-term damage
  - improve quality of life and function

Indications

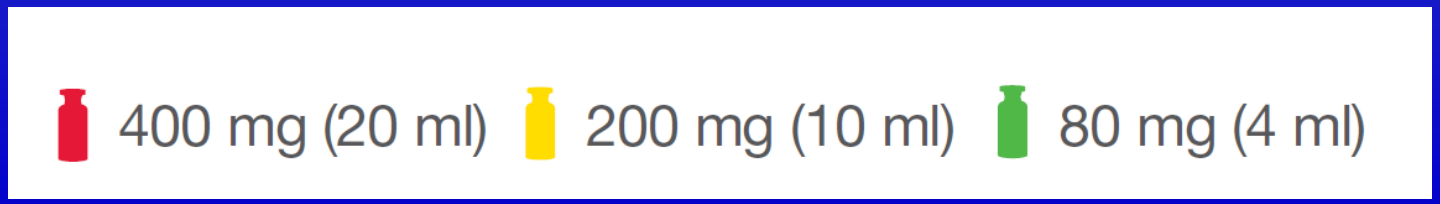
- Active SOJIA patients, ≥2 years of age who have responded inadequately to previous therapy with NSAIDs & systemic corticosteroids & MTX
- Monotherapy
  - intolerance or treatment with MTX is inappropriate
- Additional therapy in combination with MTX

Dosing & Preparations

Dosing is based on the following formulae:

- For patients weighing <30 Kg…12 mg/kg
- For patients weighing ≥30 Kg…8 mg/kg

Dosing should take place at 2 week intervals I/V



Contraindications

- Hypersensitivity to the active substance
- Active, severe infections
- Laboratory abnormalities
  - Neutropenia
  - Thrombocytopenia
  - Deranged liver enzymes

Adverse Reactions

- Common adverse reactions: (5%)
  - Upper respiratory tract infections, Nasopharyngitis
  - Headache
  - Hypertension
  - injection site reactions
- Hypersensitivity reactions….anaphylaxis(0.2%)
- Gastrointestinal perforations: 0.26%

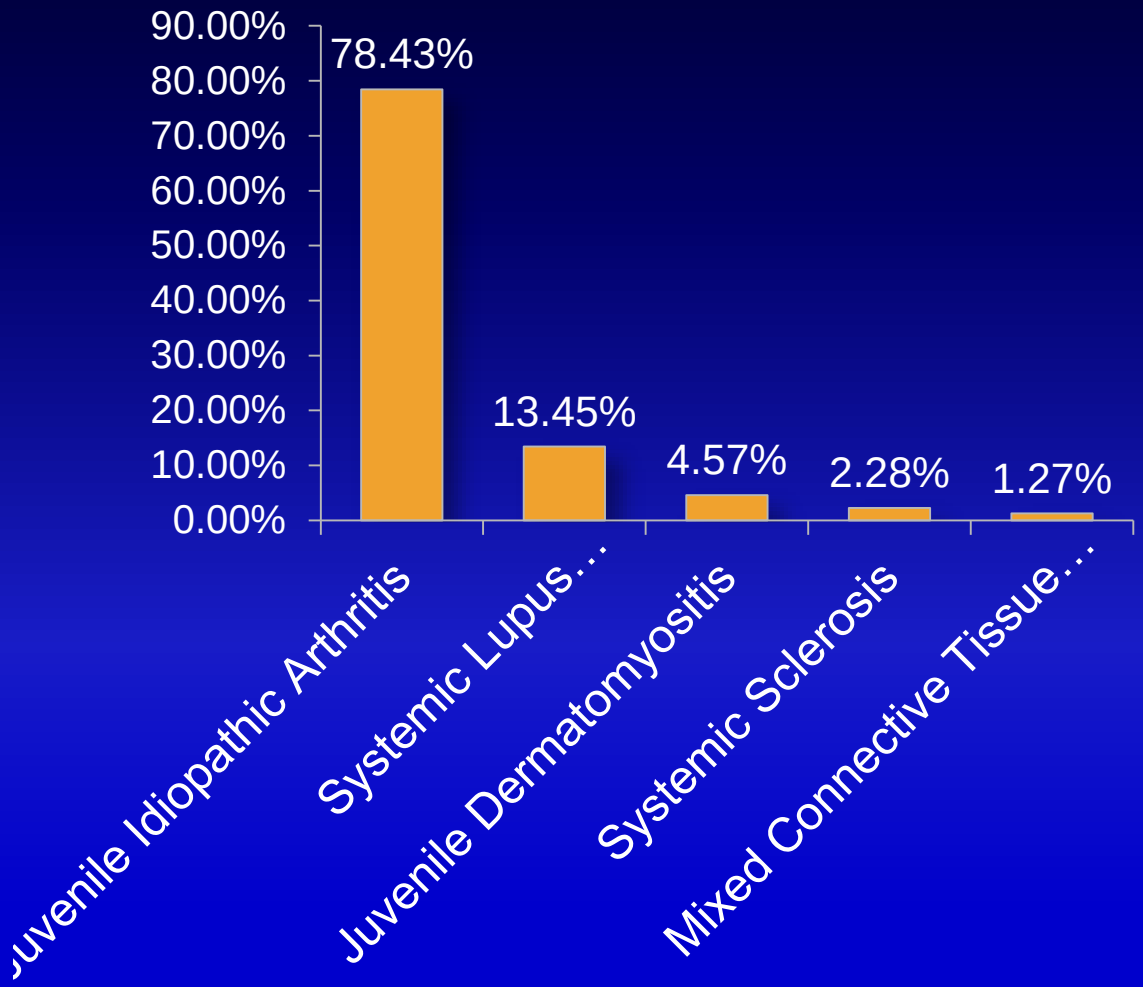
Adverse Reactions

- Serious Infections:
  - Active tuberculosis
  - Invasive fungal infections…..candidiasis, aspergillosis & pneumocystis
  - Bacterial, viral & other infections d/t opportunistic pathogens
- Laboratory abnormalities:
  - Neutropenia: (3.7%)
  - Thrombocytopenia: platelet count <100,000 /mm_3.(1%)
  - Elevated Liver Enzymes (4%)
  - Lipid Abnormalities: (0.5%)

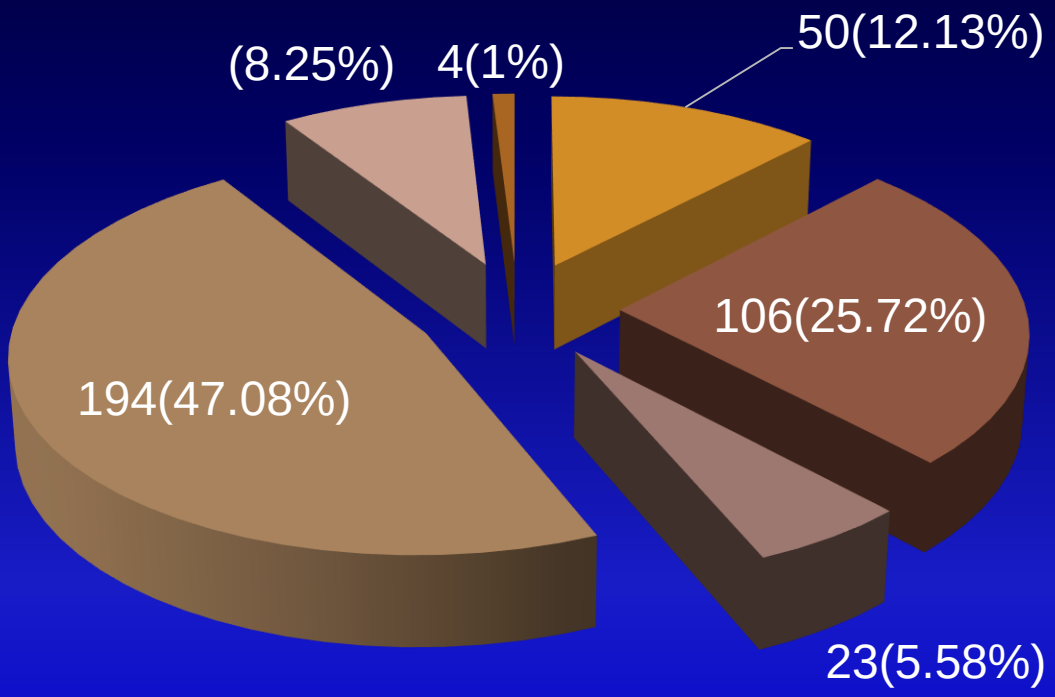
EXPERIENCE AT THE CHILDREN'S HOSPITAL & ICH, LHR TILL JAN 2014

Rheumatology Department

Common Rheumatic Diseases



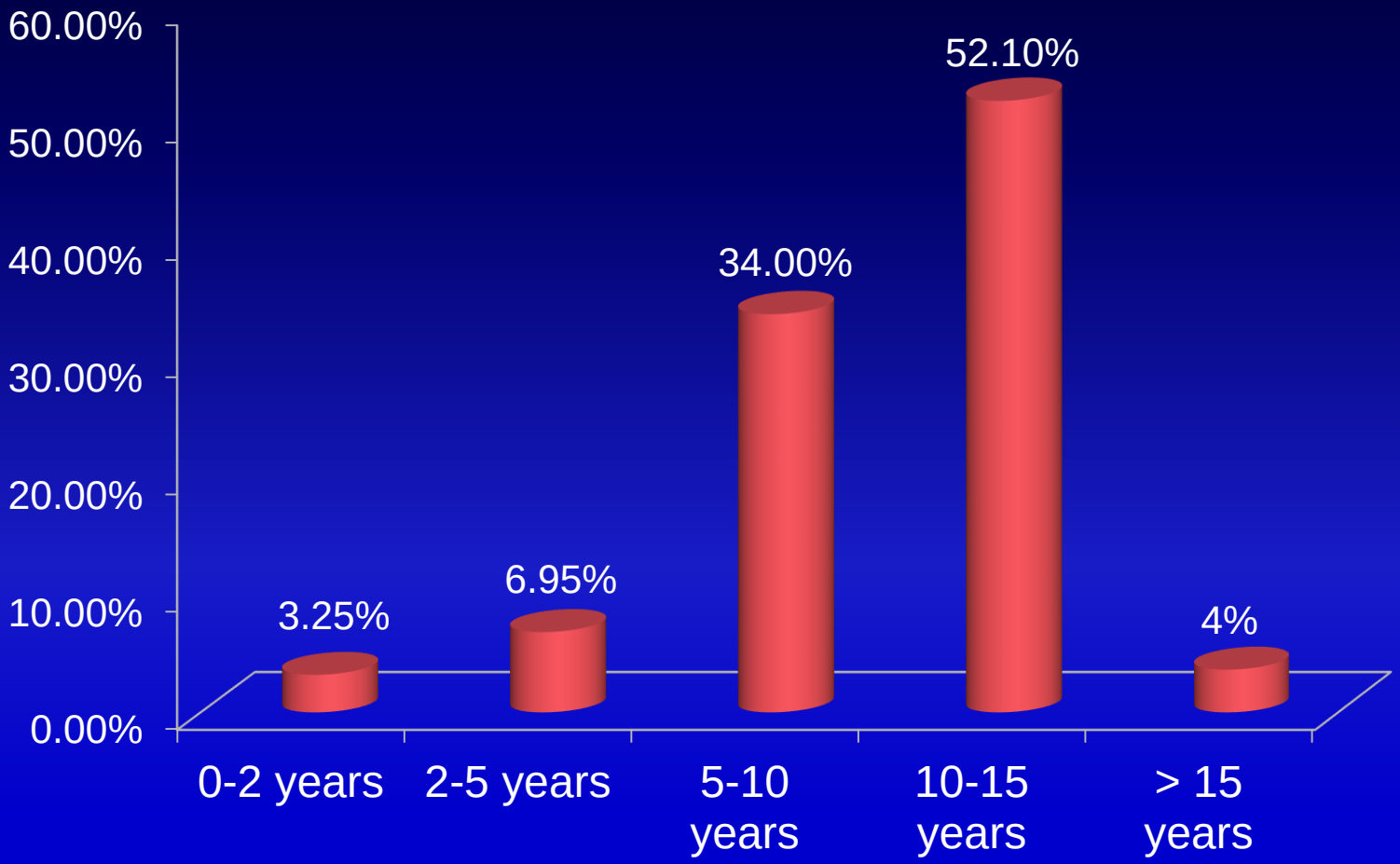
Types of JIA (n=412)



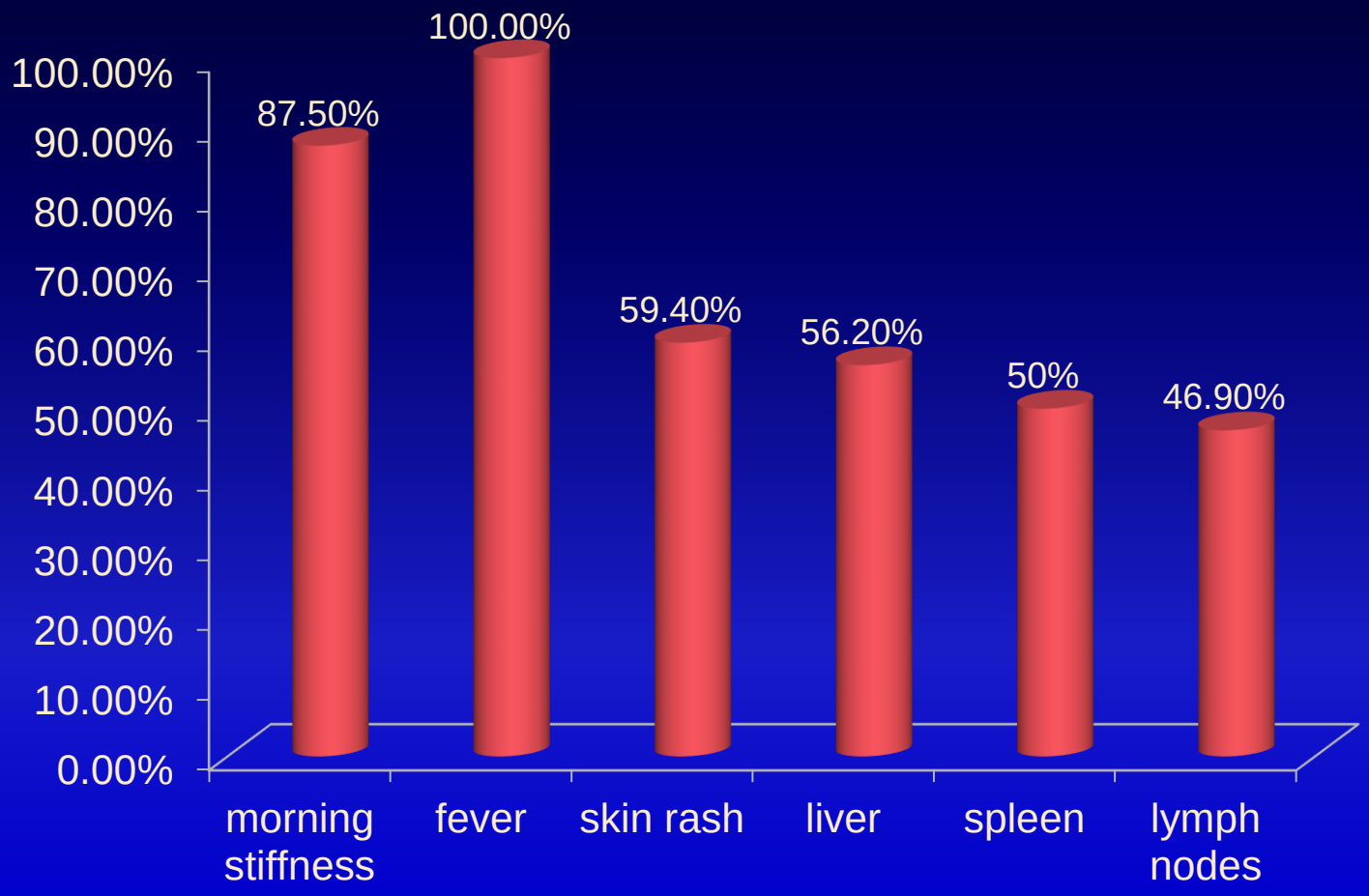
Gender distribution in JIA (n=412)

Gender	Frequency	Percentage
Male	206	50%
Female	206	50%

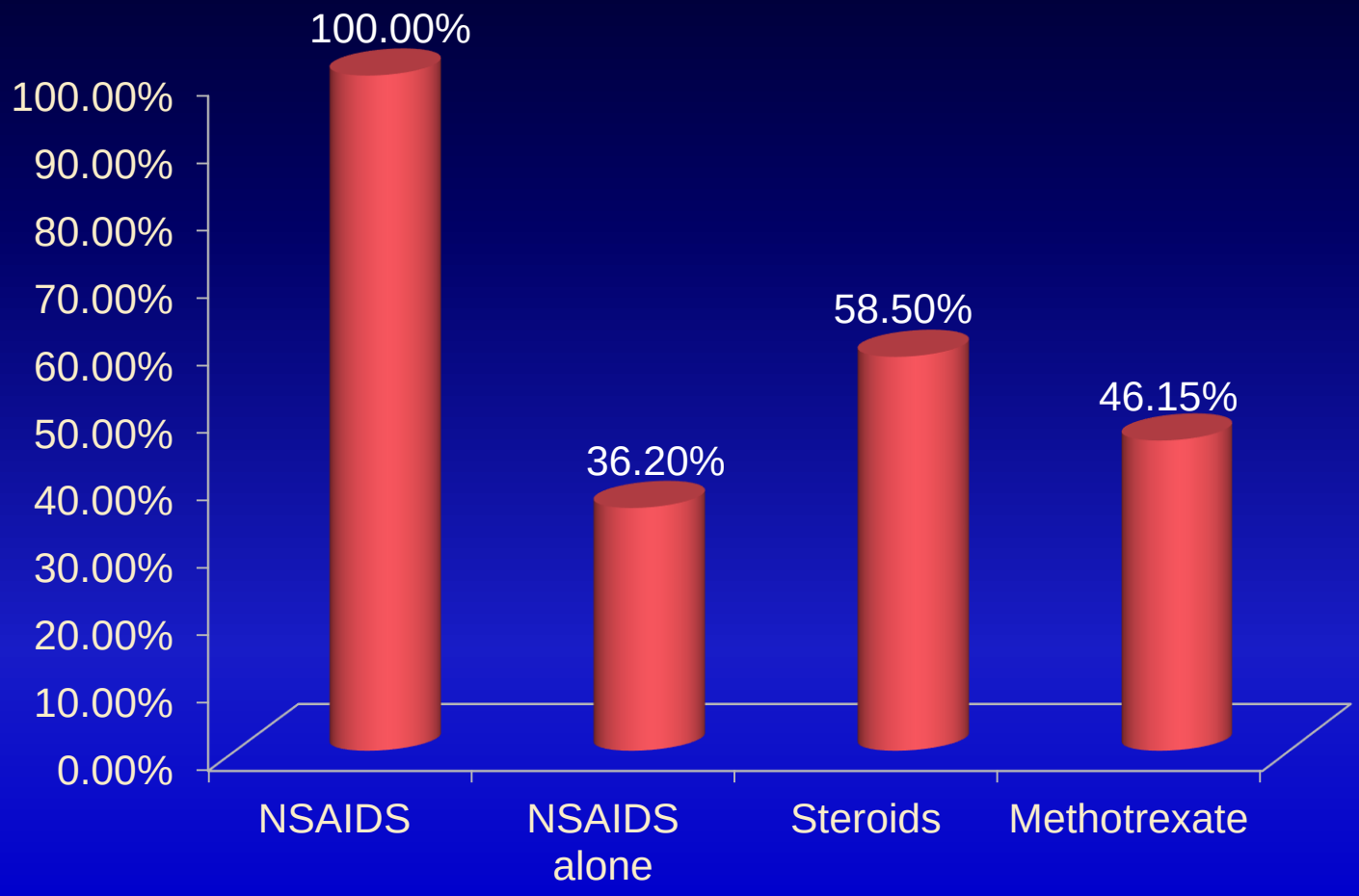
Age distribution in JIA (n=412)



Clinical Manifestations in SoJIA (n=50)

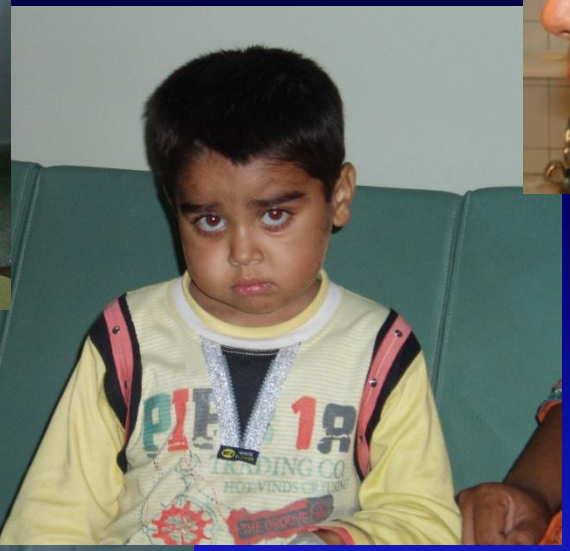


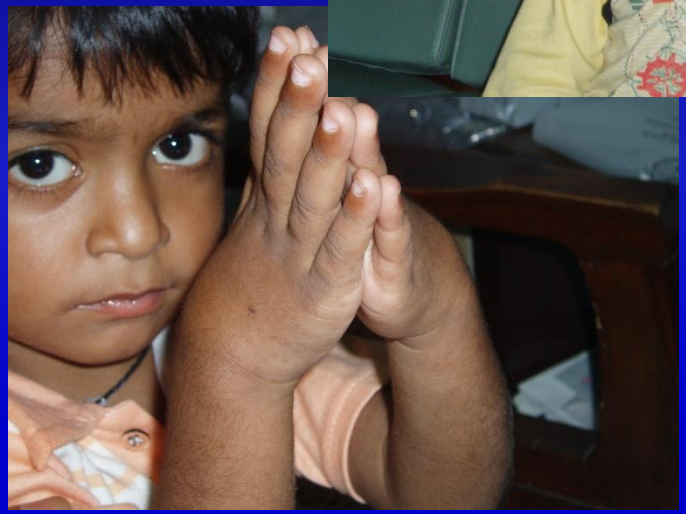
Drug used in JIA (n=412)

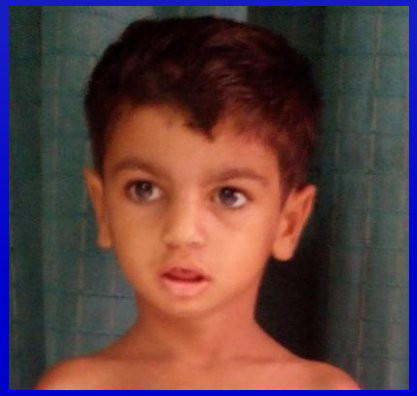


Conclusion

- SOJIA is the most severe form of JIA
- Cytokines (IL-6 & IL-1) play important role in its pathogenesis
- Less responsive to non-biologic DMARD (MTX)
- Tocilizumab (IL-6 blocker) is the future hope for these children







THANKS