A narrative review of the management of juvenile idiopathic arthritis

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This report aims to contextualise the medicines used in the treatment of the different subtypes of juvenile idiopathic arthritis and provide the rationale for current therapeutic strategies

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Preface

The paediatric Global Musculoskeletal Task Force (TF) was established in 2017 as a virtual global multidisciplinary, multi-professional and multicultural network, to advocate for the musculoskeletal health of children and young people (CYP). The TF aims to raise awareness; identify and promote tangible exemplar solutions to improve access to 'right' care; and promote healthy joints and bones by 'working better together'. A core aspect of our work is to improve access to the medicines required for the management of rheumatic diseases in CYP to better outcomes and to prevent long term disability.

This narrative review aims to contextualise the medicines used in the different subtypes of juvenile idiopathic arthritis (JIA), the most common rheumatic disease in CYP, and provides the rationale for the use of these medicines in current therapeutic strategies.

The mandate to revise Section 29 'Joint diseases in children' of the WHO EML to include triamcinolone hexacetonide for intra-articular joint injections, and anakinra (IL1-inhibitor) and tocilizumab (IL6-inhibitor) for the treatment of systemic onset JIA, in addition to the medicines already listed, is based on best available evidence for clinical practice as outlined in this review.

Our narrative review should be read in conjunction with our 'Letter of response' to the specific questions raised by our initial applications, as it provides the foundation for the arguments for inclusion of these medicines in the WHO EML. The inclusion of these three medicines to enable standard care, is supported by the network of clinicians involved in paediatric rheumatology management as evidenced by the complementary results of our two global surveys.

As the WHO EML informs many national EMLs especially in low and middle income countries, revising the WHO EML to reflect standard care, will improve access and availability of these medicines, for CYP and their families living with JIA.

Executive Summary

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory arthritis in children and has an estimated prevalence of 1:1000. The aim of management is to preserve joint structure, function, and quality of life. This is an achievable goal for many children with a multidisciplinary, targeted team approach and the advent of new classes of medicines with proven efficacy in treatment. The pharmacological management of JIA has thus been extensively revised over the last 30 years. Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, previously the mainstay of treatment, are now considered bridging agents for more long-term disease modifying anti-rheumatic drugs (DMARDs). Initial treatment with NSAIDs monotherapy is no longer recommended and aspirin, although used in other rheumatic diseases, is not the first treatment choice, due its side effect profile (hepato- and nephrotoxicity, variable tolerance, the possibility of Reye's syndrome) and the availability of alternatives. More targeted therapy such as intra-articular injections, and the early introduction of disease modifying therapy, is considered the standard of care.

Corticosteroid intra-articular injections are recommended in amenable joints, as a local, rapidly effective, systemic corticosteroid sparing strategy, with far fewer side effects. Methotrexate is still the most frequently used conventional synthetic (cs) DMARD, owing to its positive track record and low side effect profile. In approximately 20% of children, a satisfactory level of disease control is however, not achieved with csDMARDs. In these children in particular, the tremendous expansion in the number of biologic DMARDs (bDMARDs), has improved outcomes and reduced

disability dramatically. bDMARDs are most often required in the systemic onset, polyarticular, psoriatic, and enthesitis-related arthritis subtypes, as well as in refractory JIA associated uveitis. There has also been a shift to the earlier initiation of bDMARDs especially where high risk joints are affected.

There are no fewer than 16 randomised control trials reviewing the efficacy of biologics in the treatment of JIA, with 7 of these for SOJIA. The autoinflammatory aetiopathogenesis of SOJIA (different from other subtypes of JIA) necessitates a change in focus of treatment to the IL-1 family of cytokines, where medicines including anakinra and tocilizumab have shown good efficacy.

The improved outcomes are noted in long term registry data captured from multiple international cohorts. Better disease control with less overall joint damage is further reflected in the reduced number and older median age of children with JIA referred for hip and knee arthroplasty and fewer requirements for other orthopaedic procedures.

Newer targeted synthetic DMARDs include janus kinase (JAK) inhibitors. These are oral formulations as compared to intravenous or subcutaneous bDMARDs and therefore an attractive option in the paediatric population. While the JAK inhibitor tofacitinib has recently been approved for polyarticular JIA in children older than 2 years, and observational case series of JIA associated uveitis and SOJIA refractory to treatment have shown promising results, longer term studies of JAK inhibitor efficacy are still in progress.

The extent of rheumatic diseases in children including JIA, and its negative impact resulting in permanent disability, are often under-appreciated. Despite the measurable success of modern

medicines in the treatment of JIA, access may still be challenging in some regions and needs to be addressed on global platforms, to ensure the best possible outcomes.

Abbreviations

ACR	American College of Rheumatology
ANA	Antinuclear antibody
BSPAR	British Society for Paediatric and Adolescent Rheumatology
bDMARDs	Biologic disease modifying anti-rheumatic drugs
COVID	Coronavirus-19 disease
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
DMARDs	Disease modifying anti-rheumatic drugs
DOTS	Directly observed treatment short courses
EMA	European Medicines Agency
ERA	Enthesitis related arthritis
FDA	Food and Drug Administration
IAI	Intra-articular injection
ILAR	International League of Associations for Rheumatology
JAK STAT	Janus Kinase - signal transducer and activator of transcription
JIA	Juvenile Idiopathic Arthritis
LTBI	Latent tuberculosis infection
MAS	Macrophage Activation syndrome
MDR-TB	Multi-drug resistant tuberculosis
NICE	National Institute for Health and Care Excellence

NTP	National TB programs
NSAIDS	Non-steroidal anti-inflammatory drugs
pJIA	Polyarticular juvenile idiopathic arthritis
PPD	Purified protein derivative
PRINTO	Paediatric Rheumatology International Trials Organisation
psJIA	Psoriatic juvenile idiopathic arthritis
pRCT	Parallel randomised placebo-controlled trial
wRCT	Withdrawal randomised controlled trial
RF	Rheumatoid Factor
SDG	Sustainable development goals
SHARE	Single Hub and Access point for paediatric Rheumatology in Europe
SOJIA	Systemic onset juvenile idiopathic arthritis
TB	Tuberculosis

Terms and definitions

Juvenile idiopathic arthritis

A chronic inflammatory arthritis lasting more than 6 weeks, presenting before the age of 16, currently classified according to the ILAR criteria

Conventional synthetic disease modifying anti-rheumatic drugs

Immunosuppressive medications that do not target specific parts of the immune system but cause a broad cytotoxic immunosuppressive effect

Includes methotrexate (MTX), sulphasalazine (SSZ), chloroquine and leflunomide

Biologic disease modifying anti-rheumatic drugs

Monoclonal antibodies or soluble cytokine receptors which target individual components of the immune system administered subcutaneously or as an intravenous infusion. These include, but are not limited to

- TNF Inhibitors: Etanercept, Infliximab, Adalimumab, Golimumab
- Co-Receptor Targets: Abatacept
- CD19/ B Cell Targets: Rituximab, Belimumab
- IL-23 Inhibitors: Ustekinumab
- IL-17 Inhibitors: Secukinumab
- IL-1 Inhibitors: Anakinra, Canakinumab, Rilonacept
- IL-6 Inhibitors: Tocilizumab

Targeted synthetic DMARDS

Chemically synthesised small molecules which target the intracellular pathways responsible for inflammation e.g. JAK-STAT pathway inhibitors like tofacitinib, baricitinib, ruxolitinib

1. Background

Global disease profiles are shifting towards chronic non-communicable diseases, with disability adjusted life years increasing by 61.6% between 1990 and 2016. This includes musculoskeletal conditions with regional pain, musculoskeletal injury sequelae and inflammatory arthritides commonly affecting children, adolescents, and middle-aged people during their formative and peak income-earning years.[1,2]

Chronic inflammatory arthritis is a feature of paediatric rheumatic diseases and is a leading cause of long-term paediatric musculoskeletal disability worldwide. Juvenile idiopathic arthritis is the most common of these in children and has an estimated prevalence of 1:1000. It is a heterogenous group of chronic, non-infectious arthritis of unknown origin, where both genetic and environmental factors contribute to the pathophysiology. JIA occurs in children 16 years old or younger and is characterised by persistent joint swelling, pain, and limitation of movement, for at least 6 weeks. The diagnosis is made once other known causes have been excluded. JIA is a distinct entity from adult rheumatoid arthritis, differing in clinical presentations, prognosis, and treatment approaches.[34–6]

1.1 Classification

JIA is currently classified by the International League of Associations for Rheumatology (ILAR) into 7 subtypes.[7] *(Table 1)* The 6 mutually exclusive subtypes are based on differing demographics and clinical phenotypes, including the number of joints involved and serological factors. The 7th

undifferentiated subtype includes children who do not fit into any of the subtypes or have overlapping features of more than one.

The oligo-extended, enthesitis related arthritis (ERA), psoriatic and systemic onset subtypes, may also all follow a polyarticular disease course, where more than 4 joints are affected concurrently. Likewise, children with the ERA and psoriatic subtype may have an oligo-articular disease course, where 4 or less joints are affected. ANA positivity is also not exclusive to the oligo-articular subtype as there are ANA positive groups within the polyarticular rheumatoid factor negative and ERA subtypes. These challenges with the use of the ILAR classification have been acknowledged and the Paediatric Rheumatology International Trials Organisation (PRINTO) has embarked on a project to revise the ILAR classification. The working aim is to create more homogenous subtypes, and to harmonise the current subtypes with those that are similar to arthritis in adults, for use in both clinical trials and daily practice.[8] Despite these challenges and the exclusion of the spondyloarthropathies and arthritis secondary to inflammatory bowel disease, the ILAR classification continues to be used as it is considered helpful for comparing studies, risk stratification and prognostication.

The terms juvenile chronic arthritis and juvenile rheumatoid arthritis included a pauci-articular arthritis, akin to the oligo-articular JIA subtype in young girls, and a polyarticular form which encompassed ERA and psoriatic arthritis JIA subtypes, as well as the spondyloarthropathies. The definitions for systemic onset JIA have essentially remained the same. These terms are however, no longer used and the ILAR classification preferred.[3]

An awareness of the classification challenges and arthritis phenotypes is important when comparing current literature and treatment algorithms.

Table 1: ILAR Classification Criteria

Disease (Onset Type)	Criteria	Exclusions
Systemic arthritis	Quotidian fever for at least 2 weeks, documented to be daily for at least 3 days Arthritis Plus ≥ 1 of: Evanescent, non-fixed erythematous rash General lymph node enlargement Hepatomegaly or splenomegaly Serositis	Exclusions a, b, c, d
Polyarticular Arthritis RF-	Arthritis of ≥ 5 joints during the first 6 months of disease; RF- test	Exclusions a, b, c, d, e
Polyarticular Arthritis RF+	Arthritis of ≥ 5 joints during the first 6 months of disease Positive RF on at least two occasions 3 months apart	Exclusions a, b, c, e
Oligo-articular Arthritis Persistent	Arthritis of 1-4 joints during the onset or course of the disease	Exclusions a, b, c, d, e
Oligo-articular Arthritis extended	Arthritis of 1-4 joints during the first 6 months of disease Arthritis of ≥ 5 joints after the first 6 months of disease	Exclusions a, b, c, d, e
Psoriatic Arthritis	Arthritis and psoriasis or Arthritis and at least 2 of: Dactylitis Nail pitting or onycholysis Family history of psoriasis in a first-degree relative	Exclusions b, c, d, e
Enthesitis Related Arthritis	Arthritis and enthesitis or, Arthritis or enthesitis with at least two of: Sacroiliac joint tenderness and/or inflammatory lumbosacral pain Anterior uveitis that is usually associated with pain, redness, photophobia Onset of arthritis in a male after 6 years Presence of HLA B27 Family history in a first-degree relative of medically confirmed HLA B-27-associated disease - AS, ERA, sacroiliitis with IBD, Reiter's syndrome or acute anterior uveitis	Exclusions a, d, e
Undifferentiated Arthritis	Arthritis for >6 months that does not fulfil criteria in any of the above categories or fulfils criteria in more two or more categories	

Exclusions

a. Psoriasis or history of psoriasis in the patient or a first degree relative
b. Arthritis in an HLA B27 positive male beginning after the 6th birthday
c. Ankylosing spondylitis, ERA, sacroiliitis with IBD, Reiter's syndrome, or acute anterior uveitis, or a history of one of these disorders in a first degree relative
d. The presence of IGM RF on at least two occasions at least 3 months apart
e. The presence of systemic features in the patient

1.2 Extra articular manifestations

Well described extra-articular manifestations of JIA include chronic anterior uveitis in up to 30% of children with oligo-articular JIA and if undiagnosed and untreated will lead to visual impairment and blindness. Girls with oligo-articular JIA who are ANA positive and early in their disease course are most at risk, although boys have been shown to be at higher risk of uveitis complications. The challenge in these children is that the uveitis is nearly always asymptomatic in the early stages and is a lifelong condition with far reaching consequences well into adulthood. Less commonly, children with ERA may present with an acute anterior uveitis like that seen in adults, where eye inflammation causes a red painful light sensitive eye.[9,10]

Rheumatoid nodules, lung disease and cardiac disease, are rarely reported.[3]

1.3 Complications

The degree of permanent disability and the complications of JIA are somewhat dependent on disease subtype and joints involved, as well as the disease duration in relation to the initiation of

appropriate treatment. A 'window of opportunity' is thought to exist early in the disease when treatment is most effective and if initiated, results in improved outcomes.[11–13]

Prolonged, locally active inflammation may result in limb-length discrepancy due to increased blood supply to the affected epiphyses and when affecting the lower limbs can result in impaired mobility and secondary scoliosis. A more generalised growth disturbance due to ongoing active disease and often compounded by systemic corticosteroids, may also occur and result in short stature.

In the longer term, contractures, muscle atrophy, reduced bone density, bone erosions and joint destruction may develop without treatment. Joint replacement may then be needed at tremendous cost perhaps more than once in a patient's lifetime.[14,15]

The sight threatening complications from persistent or recurrent uveitis due to late diagnosis, recurrent disease flares or inadequate treatment, include cataracts, synechiae, glaucoma and band keratopathy. Importantly, uveitis causes prolonged morbidity, and irreversible loss of vision in up to 10% of children with JIA. A critical step in managing these children is screening for the asymptomatic eye inflammation and prompt treatment when diagnosed.[16] Surgery for the blinding complications of cataracts and glaucoma may often be required.

Macrophage activation syndrome is a severe, potentially life-threatening complication of systemic onset JIA (SOJIA). Due to the prolonged amplification of a pro-inflammatory cytokine cascade, the hyperinflammatory syndrome results in multi-organ dysfunction, and may cause death in some cases. Early recognition and treatment are essential.[17]

Additionally, the extensive complications of long-term systemic corticosteroid use on normal childhood development, remains an important consideration.[18] Complications include:

- Growth faltering and decreased adult height
- Osteopenia, with increased fracture risk
- Changes in body habitus
- Weight gain
- Pubertal disturbances
- Mood and sleep disorders
- Glaucoma
- Muscle weakness
- Hirsutism
- Immunosuppression
- Hyperglycaemia

Loss of school hours, travel time and expenses, costs and time spent at multiple hospital visits often contribute to loss of caregiver employment and impact on family quality of life. These are all difficult factors to measure but undoubtedly have a high socioeconomic impact and huge impact on families. Inadequately treated JIA and its complications therefore have serious implications for physical and psychosocial development, high risk of joint damage, functional disability, poor mental health which impacts long into adulthood and future levels of employment. Modern approaches to therapy and the cost implications of medicines therefore need to be addressed in the wider context of 'cost' due to lack or inadequate treatment and the huge impact on individuals, families and society.[19–24]

2. Management Overview

The pharmacological management of chronic inflammatory arthritis, typified by JIA, has advanced significantly in the last 30 years. The goal is to limit joint damage, preserve joint function and consequently, quality of life.

2.1 History

Studies on JIA cohorts from the 1980's, predominantly describe polyarticular active disease extending well into adulthood and at 30 years from disease onset, more than 50% of patients had limited mobility or were confined to bed or wheelchairs. Disability assessment, showed that 70% of patients with Steinbrocker index functional Class III to IV, had polyarticular disease.[25] The extent of irreversible joint damage was further indicated in studies assessing arthroplasty in the management of JIA, where hip and knee replacements were needed in 60% of JIA cases.[26,27] These studies reflected an era of essentially non-effective treatment, resulting in a lifetime of morbidity and in some cases, mortality.[28–30]

While overall outcomes across studies have inherent difficulties in comparison due to changes in disease classifications, the use of different outcome measures and different treatment regimens used, later studies highlight the positive impact of earlier aggressive treatment with methotrexate and other DMARDs.[31] The effects are noted by the 1990's, when an overall reduction in active arthritis 10 years after diagnosis was reported. However, active disease was still present in 22-41% with oligo-JIA, 45-50% with polyarticular JIA and in 27-48% with systemic onset JIA.[32] By the early 2000's the first bDMARD clinical trials in children with JIA were published,

with the tumour necrosis factor inhibitor (TNFi) etanercept, showing a clear reduction in disease flares in children with polyarticular JIA. This breakthrough, followed by the development and trial of other bDMARDs in children, signalled a shift in the management of JIA, to one where bDMARD therapies now play an integral role, with improved outcomes. As examples, German 2012 registry data indicated that at least 43% of children with JIA achieved inactive disease within one year compared to 20% in 2000. In 2014, a study describing a North American JIA cohort, showed that 70-90% of children achieved inactive disease within two years of treatment and had at least a 50% probability of remission without medication. Those with rheumatoid factor positive (RF+) polyarticular JIA were the exception. These children however, had a 67% probability of stopping medication at least once during the 5-year study period. csDMARDs and bDMARDs were also shown to reduce disease activity and importantly, facilitate weaning of systemic corticosteroids.[33,34]

2.2 Guidelines

The response to medicines as evaluated in clinical trials, open label studies and observational studies from long term JIA registry data as well as clinical experience, serve to inform expert opinion and goal-directed treatment algorithms for best clinical practice guidelines. A multidisciplinary team approach, including non-pharmacological management, is further advocated.[35]

These guidelines are updated as more information about the processes involved in the pathophysiology and the effect of available medicines on JIA becomes known. The clinical

phenotype, the presence of extra-articular manifestations, complications, and the involvement of high-risk joints which impact significantly on mobility and function i.e. cervical spine, wrist, hip, temporomandibular and ankle joints, are important factors noted in the therapeutic approaches.[16,36–45]

A critical appraisal of JIA management guidelines prior to 2015, highlighted some of the difficulties inherent in developing disease specific guidelines for children- paucity of evidence, extrapolation from adult studies, reliance on non-randomized controlled trials, observational studies and expert opinion, among others.[46] While the assessed guidelines were considered to have a relatively low level of evidence, the use of pharmacological agents were similar. Current guidelines acknowledge these difficulties by emphasising transparent methodologies and additionally, draw on evidence from studies with an adapted paediatric clinical trial design (e.g. randomised placebo-controlled withdrawal design). Management practices are now also underpinned by the principles as set out in the treat-to-target model of care for JIA.[47] These include:

- Setting the target, selecting the tools to define the target, and making therapeutic decisions based on individual patient characteristics, agreed on with the parents/patient
- Assessing and documenting disease activity regularly using a clinical juvenile arthritis disease activity score (cJADAS)
- Reaching at least a 50% improvement in disease activity (as measured by cJADAS) within 3 months and the target within 6 months in all patients
- Resolution of fever within 1 week, in patients with systemic JIA with active systemic manifestations

- Determining the frequency of assessments by the category of JIA, level of disease activity and presence of extra-articular manifestations. This may be
    - Weekly assessments, or a period of inpatient treatment, such as in systemic JIA with active systemic manifestations
    - Monthly to 3 monthly evaluations for patients with high/moderate disease activity, and less frequent assessments in states of persistent clinical remission
- Adjusting treatment until the target is achieved.
- Maintaining the treatment target and ongoing monitoring, once it has been achieved

The treat-to-target guidelines do not advocate for specific medicines but are focussed on the effectiveness of the treatment in achieving the therapeutic goal set by both the parent/ patient and treating physician. This is helpful in clinical practice and allows for improved, child specific care.

2.3 Monitoring of disease activity

JIA disease activity is monitored using standard assessment tools. Over the decades various tools have been used in clinical practice.[48,49] The ACR core set criteria for monitoring disease activity in JIA and the revised Wallace criteria for definitions of inactive disease and remission, have utility in clinical research and practice settings. Increasingly, clinicians and clinical studies have used the different versions of the Juvenile Arthritis Disease Activity Score (JADAS).[48,50] The JADAS has defined 'cut-off' values for low disease activity, inactive disease and remission. The 4 parameters include: active joint count (where either 10, 27 or 71 joints are assessed), patient/parent visual analogue scale (VAS) for health status, a physician/ healthcare provider VAS for disease activity

and the CRP or ESR, which are normalised to a score between 1 and 10. A clinical JADAS (cJADAS) is calculated excluding CRP or ESR. *(Table 2)*

Table 2: ACR paediatric core response variables and JADAS

American College of Rheumatology Paediatric Core Response Variables (CRV)[51]	**Juvenile Arthritis Disease Activity Score (JADAS)**[50,52]
(1) Physician global assessment of disease activity	(1) Physician global assessment of disease activity
(2) Parent/patient assessment of overall well being	(2) Parent/patient global assessment of wellbeing
(3) Functional ability (CHAQ)	*(Not included as may be more reflective of joint damage*)
(4) Number of joints with active arthritis	(3) Count of joints with active disease
(5) Number of joints with limited range of motion	*(Not included as may be more reflective of joint damage)*
(6) ESR or CRP	(4) CRP or ESR
For SJIA patients: absence of spiking fever (≤38°C during past week)	-
Definition of improvement ≥30% improvement from baseline in 3 of 6 CRVs, with ≤1 CRV worsening by >30%	Minimal Disease Activity: Cut-off values for inactive disease, minimal disease activity, moderate and high disease activity are provided for polyarticular and 0ligo-articular JIA
Definition of flare Worsening of 2 CRV by ≥40% without improvement in >1 CRV by ≥30% For SJIA, fever ≤ 38°C for at least 2 days, in preceding week, with no other cause	Definition of flare Worsening of JADAS score
Revised Wallace criteria[53] *for inactive disease:* (1) No joints with active arthritis (2) No fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA (3) No active uveitis (4) Normal ESR and/or CRP *(5)* Physician global assessment indicates no disease activity	Cut-off values for moderate and high disease activity and inactive disease, are provided for polyarticular and oligo articular JIA
Clinical remission: (1) On medication—criteria for inactive disease met for minimum 6 continuous months while patient on medication (2) Off medication—criteria for active disease met for minimum 12 continuous months while off all arthritis and uveitis medications	

Clinical remission i.e. No disease activity, with a normal physical and psychosocial functional outcome for every child is potentially achievable, as prompt access to modern management can prevent joint damage, chronic pain, and subsequent disability, with considerable improvement in quality of life.

3. Specific pharmacological management and rationale for each subtype

The differences in aetiopathogenesis between the JIA subtypes and hence the therapeutic targets are well summarised by Zaripova et al.[54] (Table 3)

Table 3: Differences in aetiopathogenesis between JIA subtypes

	Oligoarticular JIA	**sJIA**	**Polyarticular JIA**	**ERA**	**Psoriatic JIA**
Type of disease	Autoimmune	Autoinflammatory	Autoimmune	Autoimmune	Early-onset PsJIA – autoimmune, while late-onset PsJIA – autoinflammatory
Immune system mainly involved in pathogenesis	Adaptive immune system	Innate immune system	Adaptive immune system	Adaptive immune system	Adaptive immune system in early-onset PsJIA Innate immune response in late-onset PsJIA
Gene association	MHC class II	TNF, IL6, IL10, MIF, IL1	MHC class II	HLA-B27	HLA-B/C, HLAB, IL12B, IL23R, TNP1, TRAF3IP3, REL HLA-B27 in late-onset PsJIA
Antibodies	ANA	–	ANA RF, anti-CCP, anti-MCV – for RF+ JIA	ANA may be positive in some cases	ANA in the early-onset PsJIA
Predominant effector cells	$CD4^+$, $CD8^+$ T-cells, neutrophils	Monocytes, macrophages, neutrophils	$CD4^+$, $CD8^+$ T-cells	γδT-cells, Th17 cells	Th1 and Th17 cells subsets, macrophages

Key moment in pathogenesis	Imbalance between inflammatoryTh1/Th17 and Treg cells	Abnormal activation of phagocytes leads to hypersecretion of pro-inflammatory cytokines	Imbalance between pro-inflammatory Th1/Th17 and Treg cells	HLA-B27 involved in presentation of unidentified arthritogenic peptide caused T-cells activation and induction of endoplasmic reticulum stress	Autoinflammatory activation at the synovial-entheseal complex Autoimmune processes in extra-articular tissues
Main pro-inflammatory cytokines	TNFα, IL17, IFNγ	IL1, IL6, IL18, IL37, LRG and ADA2	TNFα, IL17, IL33, IFNγ	TNFα, IL17, IL23	IL17, IL23
Main treatment targets	Inhibition of T-cell proliferation, rarely anti-TNFα therapy is needed	Block of IL1 and IL6 signalling pathway	Inhibition of T-cell proliferation, block of TNFα	Block of TNFα	Inhibition of T-cell proliferation, block of TNFα

*Zaripova, L.N., Midgley, A., Christmas, S.E. et al. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatr Rheumatol **19,** 135 (2021). https://doi.org/10.1186/s12969-021-00629-8*

While there is some overlap in the antibodies and cytokines involved in the polyarticular course subtypes of JIA, SOJIA has a distinct genetic background, pathogenesis and pro-inflammatory cytokine profile.

The suggested cytokine therapeutic targets here, may also have a variable clinical effect.

3.1 Systemic Onset

Systemic onset JIA (SOJIA), also known as Still's disease, is an autoinflammatory syndrome and the most severe subtype of JIA with a significant risk of mortality.[55] SOJIA has a distinct clinical presentation including high grade quotidian fevers, rashes, organomegaly, lymphadenopathy, serositis and arthritis. The proportion of children with JIA who have SOJIA ranges from approximately 10% to 50% depending on the population, with higher rates being reported in

regions such as India and Japan.[56,57] Importantly, infections, malignancies and other rheumatic diseases including Kawasaki disease and rheumatic fever should be excluded before the diagnosis is made.

Unlike other JIA subtypes, SOJIA is mediated by the IL-1 family of cytokines, where IL-1, IL-6 and IL-18 play a central role in the pathogenesis. The disease appears to have an initial phase where IL-1 dominates, followed by high levels of IL-6, TNF-α and IL-18 with chronic polyarthritis and the potential risk of macrophage activation syndrome.[55,58] The ILAR classification includes the presence of arthritis as one of the diagnostic criteria however, SOJIA has a highly variable course with different clinical phenotypes described:

- A monophasic course of the disease with only one episode of fever and systemic symptoms *with or without* arthritis at initial presentation
- A polyphasic course with multiple episodes of fever and systemic symptoms, with arthritis at the initial presentation *or* with arthritis developing as the disease progresses
- Chronic severe polyarticular arthritis after the initial episode of fever and systemic symptoms have resolved

Although arthritis may not be clinically apparent with the initial presentation, an aggressive destructive polyarthritis will commonly develop with periods of flares and remission. Predictors of joint damage and poor outcome include young age at diagnosis (< 18 months of age), longer disease duration, persistent systemic use of corticosteroids, thrombocytosis, and high inflammatory markers. A less frequently described phenotype of SOJIA are younger children with lung disease, which may occur in the setting of macrophage activation syndrome.[59,60]

Early recognition and treatment of SOJIA is therefore essential to improve outcomes which include normal growth, and to reduce the risk of the potentially fatal macrophage activation syndrome (MAS).

Historically, patients with SOJIA were treated with high doses and prolonged courses of glucocorticoids, with significant long-term side effects such as obesity, poor growth, hypertension, cataracts, and osteoporosis. The improved understanding of the pathogenesis of SOJIA has led to significant changes in management.

Treatment of SOJIA depends on the presence or absence of MAS and/or arthritis.[40,58] (Appendix 1A)

(a) SOJIA without macrophage activation syndrome (MAS)

Initial treatment of SOJIA without MAS is variable but would include NSAIDs with or without high dose corticosteroids to manage persistent systemic signs. As soon as the inflammation is controlled (treat to target guidelines aim for no fever within a week), corticosteroids are weaned to minimise systemic adverse effects. Long-term corticosteroids are avoided as far as possible. Should there be a poor response to corticosteroids or relapse of systemic signs during weaning, biologic therapy, IL-6 (tocilizumab) and IL-1 inhibitors are suggested. These bDMARDs are advocated to minimise the severe side effects of prolonged corticosteroid use, whilst effectively controlling the underlying disease.

IL-1 inhibitors include canakinumab, anakinra and rilonacept. Anakinra is a recombinant form of the IL-1 receptor agonist and competitively inhibits IL-1α and IL-1β. It has a terminal half-life of 4-6 hours. Although not licensed for SOJIA in all countries, (it is licensed for SOJIA in Australia and

has been approved for Still's disease by the EMA) several reports describe early effective treatment with anakinra, further supporting the findings of the 2011 ANAJIS RCT, where a rapid response in patients with dominant systemic features was demonstrated.[61,62]

Canakinumab is a human monoclonal antibody that selectively binds to IL-1β, preventing inflammatory mediator production and is approved for the treatment of SOJIA. It has a longer terminal half-life of 22-25 days. Clinical trials have shown rapid and sustained clinical responses, reduced number of flares and reduced requirements for corticosteroids in the management of SOJIA. However, discontinuation rates due to inefficacy was noted in 62-81% (higher in late responders) in a long-term extension study.[63–65]

Rilonacept is a soluble receptor that neutralises IL-1β and to a lesser extent IL-1α and has a relatively shorter terminal half-life of 7-8 days. It is not commonly used in SOJIA and is not approved for this condition, however good efficacy has been shown.[66,67]

IL-6 inhibition

Tocilizumab is a humanised monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor. The terminal half-life is 14 -16 days. Tocilizumab has been shown to be effective for treating both systemic symptoms and arthritis in SOJIA, with joint disease showing radiographic improvement. Catch-up growth and improvement in quality of life have also been described.[68–72] IL-6 inhibitors are recommended by the American College of Rheumatology (ACR)[40] the National Institute for Health and Care Excellence UK,[73] and as part of a consensus based treatment strategy in Germany.[43]

Currently early IL-1 and IL-6 inhibitors monotherapy for SOJIA is considered to significantly increase the chance of remission. The early introduction of IL-1 or IL-6 inhibitors is also thought to play a role in limiting the development of a progressive arthritis. Early effective management of SOJIA, may also limit its progression to MAS. These proposed guidelines would alter previous step-up therapeutic approaches and mitigate the need for prolonged corticosteroid use.

There are few RCT's for the medicines used to treat SOJIA. Meta-analyses showed anakinra, canakinumab, tocilizumab and rilonacept to be superior to placebo, however canakinumab and tocilizumab, were more effective in the treatment of SOJIA than rilonacept. (Due to considerable differences between the RCT's, indirect analyses were performed).[74–76]

Four different consensus treatment plans (Appendix 1) were developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) to compare the effectiveness of the bDMARDs anakinra and tocilizumab, corticosteroids, and methotrexate. Initial data have demonstrated a shift to less use of corticosteroids and earlier treatment with bDMARDs. Longer term, this study will provide valuable data for the comparison of efficacy between the medicines in each treatment arm.[40,77]

Arthritis and no systemic features

Treatment of SOJIA without MAS, is further considered in terms of the predominance of systemic features or the predominance of arthritis as the disease progresses. In children where joint inflammation dominates, IAI corticosteroids are a valuable adjunct and methotrexate, with or without systemic corticosteroids is suggested as a second line treatment. Methotrexate is not

used in isolation but often in combination with a bDMARD, such as IL-6 (tocilizumab) or IL-1 inhibitors. Although TNF-α inhibitors (TNFi) are used successfully in the treatment of several subtypes of JIA, similarly to MTX, TNFi have a very limited effect, or no effect at all, on the systemic signs of the disease.[78,79] However, in the subset of SOJIA patients with well-controlled systemic features and persistent arthritis, TNFi may be more effective.[54,80,81]

Other treatment options

There is very little evidence for the use of calcineurin inhibitors like cyclosporine A, in the treatment of SOJIA. The 2013 ACR guidelines for the management of SOJIA included cyclosporine A as a third line option, should there be failure of the bDMARDs IL-1 and IL-6 inhibitors.[82] Cyclosporin A acts at cellular level and is cytotoxic to T-cells, thereby inhibiting inflammatory cytokine production. The side effects of cyclosporine A and the need for monitoring drug levels makes it a less practical option. A recent prospective observational study from India, where bDMARDs are not easily accessible, showed that cyclosporine A had about a 75% efficacy in treating the systemic symptoms of SOJIA refractory to corticosteroids, although limitations of the observational study were acknowledged.[83]

Many cytokine receptors signal through the JAK/STAT pathways, which induce transcriptional changes. JAK inhibitors can block multiple cytokines, including IL-1 and IL-6 and have a rapid onset of action. Case reports and case series have described treatment of refractory Still's disease but include few children with SOJIA. Reduction in corticosteroids use and few cases of complete resolution of symptoms were reported.[84,85] A safety, efficacy and pharmacokinetics study of

tofacitinib in paediatric patients with SOJIA is currently in the recruitment phase (NCT03000439).[86] However, until more data are available, JAKs are considered salvage medications with their role in the treatment of SOJIA yet to be defined.

(b) SOJIA with MAS

MAS in SOJIA is an acquired form of hemophagocytic lymphohistiocytosis (HLH). It is an uncontrolled, persistent 'cytokine storm' that has a fatality rate of up to 23% in SOJIA.[87] 10% of children with SOJIA develop fulminant MAS, with another 30–40% exhibiting a more subclinical form of the disease. In low resourced countries particularly, concomitant infection can trigger episodes of MAS as a serious life-threatening complication of SOJIA with high risk of mortality. Early recognition and treatment of SOJIA is particularly important in this setting, as well as exclusion or treatment of concomitant infection.[88]

The diagnosis of MAS in the setting of SOJIA is challenging. A collaborative working group including members of the ACR, EULAR and PRINTO established criteria for the classification of MAS in SOJIA, primarily for research purposes (Table 4).

Table 4: PRINTO 2016 diagnostic criteria for MAS

A patient with (suspected) SOJIA with	
Fever **AND**	
Serum ferritin	> 684 ng/ml
AND any 2 of the following	
Platelet count	<181 x 10^9/L
Aspartate aminotransferase	>48 U/L
Triglycerides	> 156 mg/dL
Fibrinogen	≤ 360 mg/dL

Laboratory abnormalities should not be otherwise explained by the patient's condition, such as concomitant immune-mediated thrombocytopenia, infectious hepatitis, visceral leishmaniasis, or familial hyperlipidaemia

While fever and high peak ferritin >684ng/ml among other lab parameters are considered to be early diagnostic clues, monitoring the trend in laboratory parameters in an individual patient is perhaps more essential for early recognition.[89]

To address some of the shortcomings of these criteria, the MAS/SJIA (MS) score[90] was developed *(*Table *5)*. The MS score includes seven parameters and differs from the 2016 classification criteria in that AST and ALT are not included and strict cut-off values are not used for laboratory variables. Instead, the values are entered into a weighted equation and are used to calculate the final score. Importantly, central nervous system (CNS) dysfunction and haemorrhagic manifestations were found to be highly discriminative between active SOJIA (SOJIA flare) and SOJIA with MAS and were included in the model along with active arthritis.

Table 5: MS score for MAS in SOJIA

Criteria	**Present=1 Absent=0**	**β-coefficient**
Neurological involvement	Present=1 Absent=0	2.44
Haemorrhagic manifestations	Present=1 Absent=0	1.54
Active arthritis	Present=1 Absent=0	-1.30
Platelet count X 10^9/L	#Value	-0.003
LDH Units/L	#Value	0.001
Fibrinogen mg/dL	#Value	-0.004
Ferritin ng/ml	#Value	0.0001
Composite score = Variable score or value times the β coefficient Score **> (-2.1)** indicative of MAS		

Other aids to diagnosis are the ESR: Ferritin ratio as opposed to ferritin alone. However, diagnosing MAS while on treatment with a bDMARD for SOJIA still remains a challenge.[91]

There are no standardised treatment protocols for MAS in SOJIA.[92] (Appendix 1A)

Based on its success in the treatment of other forms of HLH, broad cytotoxic treatment with cyclosporine A in combination with glucocorticoids is used in patients with MAS, since several case series reported rapid benefit. The side effect profile makes it a less favourable option for longer term use. As the pathophysiology of MAS has become better understood, more specific cytokine mediated treatment has replaced wider immunosuppressive therapeutic approaches. These treatments potentially include agents that inhibit IL-1, IL-6, IL-18, interferon-γ, as well as inhibitors of downstream targets of cytokine signalling e.g. JAKs. Immediate treatment with IL-1 inhibitors have been shown to be effective and anakinra as monotherapy is appropriate in patients with known SOJIA. Patients typically respond rapidly to anakinra and a poor response within 24–48 h of treatment initiation suggests the need for additional immunosuppression.[58,61] There is however, a lack of data for the use of the other IL-1 inhibitors canakinumab and rilonacept in the management of MAS. While the systemic signs of SOJIA have shown improvement with canakinumab, an early clinical trial reported episodes of MAS concomitant with its use. Although the rate of MAS was subsequently demonstrated to be similar to MAS in SOJIA without canakinumab, it is less frequently used. Several subsequent case reports have described success with canakinumab in cases refractory to anakinra. [93–95] In a RCT, rilonacept was shown to be effective in the treatment of SOJIA. One case of MAS was described secondary

to EBV infection.[67] To our knowledge further evaluation of rilonacept in MAS has not been published.

Data on JAK inhibitors in the management of MAS in SOJIA is lacking, and IL-18 and interferon gamma monoclonal antibodies are currently undergoing clinical trials for their use in MAS in SOJIA.[96–98]

3.2 Oligo-articular JIA

The oligo-articular JIA subtype is characterised by inflammation of up to four joints that continues as an asymmetrical arthritis predominantly affecting the joints of the lower extremities, such as the knee and ankle. There is a high frequency of positivity to antinuclear antibodies (ANA) and a high risk of chronic uveitis. Oligo-articular JIA is further categorised as oligo-persistent, where up to 4 joints are affected or oligo-extended JIA, where more than 4 joints are affected after the first 6 months of onset. The therapeutic approach is influenced by the sub-category and whether the affected joint/s are considered high risk.[7]

Treatment guidelines suggest intra-articular corticosteroids as the mainstay of therapy. Injectable corticosteroids have for decades been routinely used for the treatment of inflammatory arthritis and is considered the standard of care in the treatment of JIA, for joints which are technically amenable. Current ACR therapeutic approaches suggest intra-articular triamcinolone hexacetonide with or without a trial of NSAIDs as first line treatment for oligo-articular JIA. (Appendix 1B) The choice of triamcinolone hexacetonide (TH) over triamcinolone

acetonide (TA) or the more soluble depot methylprednisolone, is often limited by availability. However, TH is the preferred choice for both immediate symptom reduction and longevity of effect as compared to other preparations. Often these injections will reduce inflammation and result in good disease control in the affected joint(s) for many months and sometimes longer term for many years.[99–101] A further direct comparison of TH vs TA IAI, demonstrated an immediate and sustained effect in at least 60% of children for up to 40 months post IAI. More than double the flare rate was reported in children treated with TA at 3 months post IAI. IAI was predominantly performed in large joints in this study and mild skin atrophy and hypopigmentation were reported in 1.4%. No infections were noted.[102]

IAI is considered a relatively safe procedure with complication rates as low as 1.5-8%. Subcutaneous atrophy and fat necrosis are the most common adverse events reported, which generally resolve without intervention. In a recent global survey of intra-articular joint injection practices, iatrogenic infection was not common at 2.5% and most complications were cutaneous. No complications were reported by 18% of respondents.[103] A retrospective review of 134 patients with JIA from Ankara, showed the median duration of remission to be 15 months (range 1-64 months). IAI was demonstrated to be a safe procedure with 1.5% experiencing mild cutaneous side effects. Cushingoid reactions and joint infection did not occur. Triamcinolone hexacetonide was used in larger joints and methylprednisolone for smaller joints in this study.[104]

While TH is a particular consideration in large joints, a more soluble corticosteroid may be an alternative in small or superficial joints (betamethasone or methylprednisolone) to avoid

subcutaneous atrophy or hypopigmentation. However, access to medicines needed to perform the IAI and facilities to perform the procedure may be limiting factors. In 2005 Gondwe et al described a case series of 9 children (<5%) who developed Cushing's syndrome post IAI with TA. Higher total doses of more than 100mg (up to 14.5mg/kg), and 2 cases with additional oral corticosteroid were described. It was reported that similar doses with TH were used previously *without* the development of Cushing's syndrome and that TH was considered more effective.[105,106]

Systemic corticosteroids as part of initial therapy were recommended *against* in the current ACR therapeutic approaches, to mitigate systemic side effects. The caveat was suggested to limit use to the shortest possible duration and the lowest effective dose for situations where intra-articular injections were not possible, and the rapid alleviation of symptoms needed. This approach is supported in other guidelines. Imaging guidance for joints that are difficult to access, or to localise the inflammation is suggested where available.[35]

Some children may need repeat injections or be treated with csDMARDs. Escalation to DMARDs like methotrexate is considered to bring about optimal disease control, should there be no improvement. Methotrexate is the second line treatment of oligo-articular JIA poorly responsive to IAI, owing to the preponderance of evidence for its safety and efficacy. Route of administration is at the discretion of the treating physician. As there is a lack of comparator trials, and tolerability to methotrexate is variable, other treatment options such as leflunomide, sulfasalazine and

chloroquine are provided in guidelines, even though the evidence for their use in this setting is low.

The decision to accelerate therapy to a bDMARD is based on a poor response to methotrexate and additional factors which include affected high-risk joints (e.g. sacro-iliac and temporomandibular joints), the presence of erosive disease, raised inflammatory markers and symmetric disease, and JIA associated uveitis. These are used to guide the choice of biologic, with TNFi commonly the first option. Biologics are not often needed for arthritis control in the oligo-persistent subtype but may be required to manage the associated uveitis. TNFi may also be needed to treat the oligo-extended subtype, which is grouped with the management of polyarticular JIA. Tocilizumab and abatacept are suggested as third line therapy if there is a failure to respond to TNFi, although the level of evidence is low.

3.3 Oligo-extended, Polyarticular JIA RF-, Poly-JIA RF+

Polyarticular JIA (pJIA) affects five or more large/ small joints and inflammation of the metacarpophalangeal joints and wrists is common.

Both RF-positive and negative subtypes have characteristic clinical features. In RF-negative pJIA, inflammation can be asymmetrical, but for RF-positive pJIA symmetric involvement of the large and small joints of hands and feet is the more common. Indicators of more aggressive disease include RF and anti-citrullinated peptide positivity and joint damage at presentation.

The initial management of polyarticular JIA considers NSAIDs as a bridging agent for more long term DMARDs. Methotrexate is suggested over other DMARDs like leflunomide, chloroquine or

sulfasalazine, and intra-articular corticosteroids are viewed as adjunctive therapy. In low disease activity, a change in DMARD to methotrexate if not yet used is recommended. However, in moderate to high disease activity, escalation to a biologic (TNFi, abatacept or tocilizumab) over a change to a second DMARD is preferred. Should a high disease state persist, a change after primary failure of TNFi to either abatacept, tocilizumab or rituximab should be considered. The usual step-up approach may be adjusted in patients where high risk joints are affected and where disabling joint damage is a concern. While studies exploring the potential role of initial biologic treatment have shown early improvement in disease activity, the longer-term outcomes appear to be similar, hence initial biologic DMARDs are only considered in severe extensive disease and with high-risk joint involvement. However, the treat-to-target principles still apply.[107–111] (Appendix 1C)

Other treatment options under consideration include JAK inhibitors.

A RCW trial of the JAK inhibitor tofacitinib in the treatment of polyarticular JIA, met its primary endpoint of lower JIA flare rate by week 44 and reported improvements in secondary endpoints related to disease activity and physical function. Importantly, only 4 of 225 cases of serious infection were reported.[112] However, further study is required to confirm these results and long-term safety in clinical practice.

3.4 Enthesitis Related Arthritis (ERA)

Enthesitis-related arthritis (ERA) presents with enthesitis (inflammation at the point of tendon or ligament insertion on bone) and may resemble oligo– or polyarthritis of the joints of the lower

limb. The pathogenesis of ERA is driven by HLA-B27-mediated presentation of arthritogenic peptide following T-cell activation, and IL-23 and IL-17 secretion. Enthesitis is triggered by repeated biomechanical stress resulting in microtrauma and release of molecular components from damaged connective tissue. This may directly activate synovial macrophages, stromal cells, and IL-23 production, and establish a positive feedback loop. Due to lower limb and sacroiliac joint involvement, enthesitis, uveitis and the association with HLA-B27, it has been suggested that ERA is a disease that belongs in the group of spondyloarthropathies.[113] The management of the oligo- and polyarthritis follows the principles as described in those sections (above), including the management of high risk joints. Of note, plain radiography is not sensitive enough to assess joint inflammation and enthesitis in children and may delay clinically appropriate imaging and treatment. Advanced imaging including MRI is necessary to identify active synovitis or enthesitis.[35] Sacroiliitis (an arthritis involving a high-risk joint), merits the early consideration of a bDMARD. Treatment with TNFi as the preferred first line agent is advocated in this setting. While methotrexate monotherapy and sulphasalazine are not recommended in ACR guidelines, it is conceded that methotrexate plays a role in treating peripheral arthritis, that sulfasalazine is an alternative in patients who have bowel inflammation and in those with contraindications to TNFi.

The treatment of enthesitis similarly involves NSAIDs, short term bridging with corticosteroids, intra-articular corticosteroids, and methotrexate. The TNFi adalimumab and etanercept have proven effective in ERA and should be considered when there is lack of improvement or earlier, when high risk joints are affected (Appendix 1B, 1C).

Interleukin-17A (IL-17A), is an important cytokine involved in the inflammation of ERA and psoriatic arthritis (PsA). Secukinumab, a monoclonal antibody that directly inhibits IL-17A, has recently been licensed for children with ERA aged 4 years and older, following the results of the three-part, double-blind, placebo-controlled, randomised-withdrawal JUNIPERA trial.[114] Efficacy was demonstrated with a significantly longer time to disease flare vs placebo, sustained improvement of signs and symptoms up to Wk 104 and a favourable safety profile were also demonstrated. These data are supported by clinical trials in adults with spondyloarthropathies. The ongoing open label extension trial will inform future clinical practice.

Ustekinumab is a monoclonal antibody directed against the shared p40 subunit of IL-12 and IL-23, critical for the development of TH17 cells. An open-label study of ustekinumab in adults with ankylosing spondylitis demonstrated an Assessment of Spondyloarthritis International Society (ASIS) 20 response in 60.1% of subjects, as well as improvements in imaging findings of arthritis and functional outcomes.[115] Ustekinumab showed superiority in clearance of enthesitis when compared to TNFi in the randomised controlled open label ECLIPSA study.[116,117] A case series of 5 children with refractory ERA, i.e. failed multiple TNFi and csDMARDs, also showed an improvement in active joints, resolution of clinical sacroiliitis in 3 and subjective improvement of pain in 4.

However, there are no double blind RCTs published for ustekinumab in ERA at the time of writing.

3.5 Psoriatic (PsA)

Psoriatic arthritis can vary widely in presentation and severity. Cutaneous psoriasis may be occult, overt, or not be present at all. The extent of articular involvement may vary from mild enthesitis, oligo-arthritis, to polyarticular involvement of multiple axial (spine, sacroiliac joints) and peripheral joints. Small joints are affected and accompanied by dactylitis, and/ or nail pitting. Psoriatic JIA itself is described as a heterogeneous disease where children < 6 years are more likely to be female, ANA-positive and predisposed to chronic uveitis, with arthritis of wrists and small joints of the hands and feet. Early-onset psoriatic JIA is characterised by the development of dactylitis caused by dysregulation of adaptive immune mechanisms. In older children disease is associated with HLA-B27 positivity, enthesitis and axial disease with male predisposition. The pathogenesis of late-onset psoriatic JIA resembles ERA with enthesitis and bowel wall inflammation. Since no randomised controlled trials have been conducted in children with psJIA, treatment guidelines are derived from trials in other JIA subtypes and from adult psoriatic arthritis.[118] The management of psJIA depends on the clinical phenotype and follows the same principles as previously set out for oligo- or polyarticular arthritis(Appendix 1B, 1C). As in ERA, the JUNIPERA IL-17A inhibitor trial showed a significantly longer time to disease flare and sustained effect up to Wk 104 in psJIA.

Future treatment options for consideration include ustekinumab, currently licensed for paediatric psoriasis. A phase 3 multicentre, open-label study to evaluate the efficacy, pharmacokinetics, safety, and immunogenicity of subcutaneously administered ustekinumab or guselkumab in paediatric participants with active juvenile psoriatic arthritis (PSUMMIT-Jr) NCT05083182, is currently in the recruitment phase.

3.6 Undifferentiated JIA

Children categorised as undifferentiated JIA may either fulfil ILAR criteria for more than one subtype or have clinical manifestations which do not fulfil the requirements of a single subtype. There is often an overlap between the criteria for the polyarticular JIA RF negative and ERA subtype, and psJIA. The treatment algorithms and principles for the presenting clinical phenotype are generally followed.

3.7 JIA associated uveitis (JIAU)

JIAU occurs in up to 30% of children with JIA and can be an acute or chronic disease. The Standardisation of Uveitis Nomenclature (SUN) criteria are used to define the anatomical location and time course of uveitis, allowing reproducible assessment and monitoring of disease.[119]

Acute anterior uveitis is episodic, unilateral, and is characterised by the sudden onset of erythema, pain, and photophobia. Typically associated with HLA–B27, it occurs in children with enthesitis-related or psoriatic arthritis. The response to ocular corticosteroids is usually more definitive and escalation to systemic treatment may be required for the underlying arthritis.

Chronic anterior uveitis (CAU) differs in that it is usually asymptomatic and there is rarely external evidence of inflammation. Early detection through regular screening of at-risk children and appropriate treatment can prevent complications and improve visual outcomes. Children diagnosed at a younger age, and who are ANA positive are at increased risk of developing chronic

anterior uveitis. This form of uveitis is most frequently associated with oligoarticular and rheumatoid factor negative polyarticular JIA subtypes, as well as the subgroup of ERA, where ANA is positive. Three monthly screening for asymptomatic disease in these patients is suggested in the recent SHARE, ACR and French guidelines, with regular ophthalmology review once diagnosed and treatment commenced.[16,120,121] Local ocular corticosteroid drops are the first line of treatment, followed by subcutaneous methotrexate should there be no improvement after at least 3 months of sustained therapy. With an ongoing requirement for corticosteroids, the next line of therapy are the TNFi, where current evidence suggests better efficacy of adalimumab, over infliximab and golimumab. Adalimumab has a proven record of efficacy based on 2 clinical trials (SYCAMORE and ADJUVITE).[122,123] Etanercept is avoided in the treatment of CAU as previous studies have shown no effect on CAU and episodes of relapse were reported in spite of its use. A poor response to adalimumab, due to the development of neutralising antibodies or lack of efficacy, obviates a change to a second TNFI before a different class of biologics is considered (eg. tocilizumab, abatacept, rituximab). However, tocilizumab [124,125] may be considered earlier in the treatment algorithm should macular oedema be present. Most open label case studies evaluating these agents have been conducted in patients with severe refractory CAU, where multiple agents have failed, so the efficacy may be underestimated (Appendix 1D).

JAK inhibitors have also been described in a few reports to improve ocular inflammation, visual acuity and macular oedema and an open label multicentre trial *(JUVE BRIGHT)* is currently underway to review the efficacy of baricitinib in CAU.[126,127,128]

4. Risks of treatment options

The mechanism of action of the medicines used to treat JIA may confer an increased risk of adverse events. Baseline testing prior to the commencement of therapy is needed to assess for any contra-indications and ongoing monitoring on treatment is essential. This should ideally include a full blood count and differential, liver and renal function tests, lipid profile, the exclusion of latent tuberculosis, as well as urinalysis. The side effects and risks associated with each class of medicine are well described, with appropriate monitoring for each medicine tabulated below (Table 6).[35]

Immunosuppression due to underlying JIA is known to increase susceptibility to infection. This is exacerbated by corticosteroid doses of >10mg/day, and has been reported to be independent of methotrexate and TNFi use. Mostly upper respiratory tract infections related to bDMARD have been reported. Meta analyses of serious SAE have shown no differences between placebo and IL-1 inhibitors, although tocilizumab and canakinumab showed increased risk of infection.[76,129,130]

Tuberculosis

Tuberculosis is an important cause of morbidity and mortality globally, especially in areas of high prevalence, where HIV, malnutrition, and the advent of MDR-TB hamper efforts to improve outcomes. In line with the WHO End TB 2035 strategy and the subsequent formation of the Child and Adolescent TB Working Group, member countries have committed to intensifying efforts to eradicate TB by 2035 - Active contact tracing, regular follow up and community or health centre-based directly observed treatment short courses (DOTS), are approaches which contribute to the

implementation of the regional framework for action.[131,132] However, survey results of current practices and barriers to the implementation of strategies to combat latent TB infection (LTBI), report that active TB cases remain the priority and programs for the identification and management of LTBI are either non-existent or comparably less focussed. Screening tools used included (where available) tuberculin skin tests, chest X-Rays, interferon gamma assays, molecular tests, and health symptom questionnaires. Limited availability of PPD and IGRA test kits (as these are not always domestically produced), the impact of the COVID pandemic on molecular tests where resources were redirected, the high cost of diagnostic testing (IGRAs, molecular tests) and the lack of infrastructure were further reported as barriers to the successful implementation of LTBI testing programs.[133] Additional challenges in children and adolescents include under-detection, under-reporting of cases and of contact tracing, few preventive TB treatment services, and lack of integration between TB programs and child health services. Yet, tuberculosis is preventable and effective treatment is widely available. Updated WHO guidelines for national TB programs (NTP) on the management of child and adolescent TB have been published, and are complemented by the Defeat Childhood TB project, which outlines key policy recommendations for NTP to strengthen childhood and adolescent TB services; one of which is to scale up TB preventive treatment in at risk children.[134] Children with JIA are an at-risk group and additionally require screening for LTBI due to immunosuppression.[135] It is mandatory to screen all patients for LTBI before starting treatment, using available screening tools. This is emphasised in a paper of consensus statements on JIA care in low resourced settings as level 3b evidence, strength A statement, with 100% consensus. It is also recommended that JIA patients

with a positive PPD or QuantiFERON test should be managed appropriately for tuberculosis (as per current national guidelines):

- Before the start of biologic therapy
- When on biologic therapy and a previously negative PPD converts to positive at the mandatory annual tuberculosis screening, or
- If a new exposure to tuberculosis is reported.

Healthcare workers in contact with children diagnosed with JIA should remain vigilant. A high index of suspicion should be maintained, 6-12 monthly mandatory LTBI screening performed *in addition* to regional guidelines in high prevalence regions, with a low threshold for starting treatment. Patients and parents/caregivers should be educated about suspicious symptoms and protocols to follow in cases of known exposure.

Treatment of LTBI and possible longer-term prophylaxis in higher risk groups is essential for the safe use of bDMARDs. Guidelines for the management of LTBI in JIA patients have been developed.[42,132]

Table 6: ACR 2021 Management of treatment side-effects and risks

Medicine side effect/ risk	Action/ Prevention/ Monitoring
Systemic corticosteroids ● High dose, prolonged use of corticosteroids (>15 days) ● Immunosuppression ○ increased risk of infection -increased susceptibility, deterioration of existing infection and unmasking latent infection ○ Anti-inflammatory effects may mask symptoms of infection and delay diagnosis and treatment ● Hyperglycaemia ● Behavioural change - insomnia, mood changes ● HPA axis suppression - risk of adrenal crisis ● Weight gain ● Growth retardation ● Cushingoid features ● Hypertension ● *Avascular necrosis	● Avoidance of long-term systemic corticosteroids where possible ● Limit to short courses where needed ● Ensure adequate immunisation ● Monitor blood glucose, blood pressure
NSAIDs (all) ● GI Bleeding risk ● Liver toxicity ● Renal toxicity	● Monitoring via CBC counts, LFTs, and renal function tests every 6–12 months ● Enquire about GI side effects, short term use proton pump inhibitors
Methotrexate ● Fatigue, swollen gums, decreased appetite, hair loss, oral ulcers, headache, diarrhoea, vomiting ● Anticipatory nausea ● Abnormal liver functions ● Bone marrow suppression ● Infection	● Use of folic/folinic acid with methotrexate may mitigate adverse events and improve tolerability ● Anti-nausea medication ondansetron, switching the route of administration or behavioural interventions may be tried[136] ● Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months ● Decreasing the methotrexate dosage or withholding methotrexate if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found. ● Adequate vaccination
Leflunomide ● Abnormal liver functions ● Bone marrow suppression ● Infection	● Altering leflunomide administration if a clinically relevant elevation in LFT results occurs (temporary withholding of leflunomide if the ALT level is >3 times the upper limit of normal [ULN]) ● Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter

Sulfasalazine ● GIT disturbance ● Stevens -Johnson syndrome ● Hepatotoxicity	● Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter ● Decreasing the sulfasalazine dosage or withholding sulfasalazine if a clinically relevant elevation in LFT results or decreased neutrophil or platelet count is found
Hydroxychloroquine ● Retinal maculopathy after prolonged use	● Monitoring via CBC counts and LFTs annually ● Baseline and annual retinal screening after starting hydroxychloroquine
TNFI ● Bone marrow suppression ● Abnormal liver functions ● Infections	● Monitoring via CBC counts and LFTs annually at a minimum, though more frequent monitoring if methotrexate also used ● Consider TB prophylaxis and screening in high-risk regions
Tocilizumab ● Bone marrow suppression ● Abnormal liver functions ● Raised cholesterol ● Infections ● Injection site reaction ● Infusion reaction	● Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter ● Monitoring of lipid levels every 6 months ● Altering tocilizumab administration is if monitoring reveals elevated LFT results (if 1–3 times the ULN, decrease the dosage or increase the interval between doses, if >3 times the ULN, withhold administration, if >5 times the ULN, discontinue treatment), neutropenia (500–1,000/mm^3), or thrombocytopenia (50,000–100,000/mm^3) ● Consider TB prophylaxis and screening in high-risk regions ● Ice pack, local topical anaesthesia ● Pre-medication with antihistamine, paracetamol and/ or corticosteroid
Abatacept ● Infections: bacterial and opportunistic	● Doing no routine laboratory monitoring is conditionally recommended (ACR) ● Concomitant drug use would be an indication for monitoring
IL-1 inhibitors **Anakinra, Canakinumab, Rilonacept** ● GIT disturbance ● Abnormal liver functions ● Hyperlipidaemia ● Infections	● Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter ● Lipid profile at least annually ● TB prophylaxis and screening
Tofacitinib ● Bone marrow suppression ● Abnormal liver functions ● Abnormal lipid profile ● Infections	● Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter ● Monitoring of lipid levels 1–2 months after starting treatment ● Altering tofacitinib administration is strongly recommended if monitoring reveals laboratory abnormalities of concern.

	Specifically, medication should be discontinued if the haemoglobin level is <8 gm/dl or decreases by >2 gm/dl, or for severe neutropenia (<500/mm^3) or lymphopenia (<500/mm^3) ● Consider TB prophylaxis and screening
Rituximab ● Infusion reaction or hypersensitivity ● Infections, upper respiratory tract infections ● Lymphopaenia ● Hepatitis B reactivation	● Careful monitoring during subsequent infusions ● Slower infusion rate ● Rituximab desensitisation ● Monitoring CBC and differential count 1-2 months after infusion and every 3-4 months thereafter ● Monitoring CD19 count ● Appropriate Immunisation ● Consider prophylaxis to P. jirovecci

**AVN is associated with high-dose oral or intravenous corticosteroid therapy exceeding 20 mg of prednisone per day for extended periods of time, rather than intra-articular corticosteroids per se. There is also a cumulative dose risk that has not yet been clearly defined. Evidence suggests a multifactorial process that results from an imbalance in bone resorption and repair, compromise of vasculature, and both direct and indirect bone cell apoptosis.*

4.1 Intra-articular injections

Although systemic and local adverse reactions between 2-8% have been reported, it is significantly less than when systemic corticosteroids are used. A recent study of TH vs TA reported an adverse event rate of 1.4%, which were cases of subcutaneous atrophy and lipodystrophy.[102] In a 2021 PRINTO survey of joint injection practices, 18% had not observed any adverse events with IAI.[103]

Table 7: Intra-articular corticosteroid adverse events

Adverse event[137]	**Cause**	**Prevention/ Action**
*Subcutaneous atrophy	Extravasation of corticosteroid into surrounding tissue	Transient- resolves spontaneously Minimise leakage by: Confirm position of needle in joint by aspiration, or imaging e.g. joint ultrasound Injection of local anaesthetic to clear needle and track
**Steroid lipodystrophy	Extravasation of corticosteroid into surrounding tissue	Transient- resolves spontaneously Use more soluble preparations in smaller joints e.g. methylprednisolone acetate Smaller dose i.e. 0.5mg/kg for smaller

		joints
Pain post injection	'crystal synovitis'	Transient/ Rare Injection of local anaesthetic after corticosteroid Oral analgesia post procedure
Calcium deposition in joint		Resolves spontaneously Visible on radiographs Does not interfere with function
Systemic Absorption	Multiple joints injected	Less common Careful consideration of intra-articular steroid preparation, less soluble preparation preferred TH>TA>MP Consider number of joints, dose, and frequency of IAI
Infection (septic arthritis at injection site)	Poor aseptic technique	Strict adherence to aseptic technique Avoid injecting over areas with obvious infection or open wounds
Avascular necrosis (hip)		Very rare- theoretical risk (<10 cases in adult literature) Confirmation of dose and careful monitoring post IAI

**Subcutaneous atrophy resolves over time in most patients but can persist in some cases.*
***Steroid lipodystrophy is rare, but is more common over fingers, toes, wrists and ankles and subtalar joints where joint access is technically more difficult, or the joint space is limited*

4.2 TNFi (including etanercept, infliximab, adalimumab, golimumab)

Localised injection site reactions are common with both adalimumab and etanercept and can occur in up to one-third of patients. These reactions tend to lessen with time and may be present for up to two months. The use of ice packs before and after injections

and local anaesthetic cream may be useful in managing discomfort. In more severe reactions topical corticosteroid cream can be considered.[138]

Infliximab is a chimeric molecule of human and murine origin and carries the risk of more serious hypersensitivity reactions and even anaphylaxis as it is given intravenously. This agent should therefore be given in facilities where therapy for this eventuality is readily available. In some cases, pre-treatment with antihistamines and corticosteroids may be useful. Anti-drug antibodies

may develop to all these agents, leading to loss of efficacy. Methotrexate is not only synergistic in terms of efficacy but may also help to reduce the development of anti-drug antibodies (ADAs) which have a neutralising effect.[139,140]

Increased infection risk

Patients on TNF inhibitor therapy have higher rates of infections, especially upper respiratory tract infections, otitis media, bronchitis, and tonsillitis. There is also an increased risk of severe infections in patients taking these agents, especially with the monoclonal antibodies. [141]

In lower resourced countries the risk of TB is a particular concern as discussed previously.

In children the increased risk for varicella zoster infection is a significant concern and pre-emptive immunisation guidelines should be considered in unexposed and unimmunised children before the start of therapy.[142]

Risk of cancer

In 2010 the Federal Drug Administration (FDA) published a warning citing a study which investigated reported cancers for children on anti-TNF therapy in the FDA database.[143] This study compared the risk of cancer to the healthy population, and not to JIA patients (not on TNF inhibitors), who are known to have a slightly higher risk of malignancy than the healthy population. Most long-term registries in children with JIA do not show a risk of cancer greater than the existing risk for children with JIA on methotrexate. These studies note that only longer term, prospective data, with large numbers of patients will be able to adequately assess the true risk for malignancy in children on biologic therapies.[144,145]

An aspect of TNFi treatment that is sometimes discussed, is the risk of developing other autoimmune conditions. Children with JIA have an increased prevalence of autoimmune disease as compared to the general population, TNFi treatment notwithstanding. However, an evaluation of the CARRA database showed a threefold increase in the risk for developing new onset psoriasis, with the highest incidence following, or concurrent with adalimumab treatment. Switching to another TNFI may resolve the issue although a change of biologic class is sometimes required.

Anecdotal reports of increased prevalence of autoimmune diseases in children with JIA including SLE, glomerulonephritis, thyroiditis, vasculitis, and interstitial lung disease have also been published.[146,147]

4.3 IL-6 inhibitor (Tocilizumab)

The most common adverse effects with tocilizumab appear to be related to infections of the respiratory tract and gastrointestinal tract. Infusion reactions are not uncommon and can range from mild to severe. Neutropenia has also been reported. Awareness of tuberculosis risk in patients treated with tocilizumab and other bDMARDs is of particular importance in low resource settings with high rates of tuberculosis. Although TB risk has not been identified as a specific concern, all patients should be tested for tuberculosis prior to commencing tocilizumab, as for TNFi and as determined by regional infectious diseases guidelines. It has been shown that those who are younger, with short stature, lighter weight, and high disease activity in the early stages of tocilizumab administration are more likely to react to the medication. Pre-medication to

minimise the risk of an infusion reaction, such as intravenous hydrocortisone and/or an antihistamine, would be appropriate in children with these risk factors.[148]

4.4 IL-1 inhibitors (Anakinra, Canakinumab, Rilonacept)

IL-1 agents are generally safe and well tolerated. The risk of infection, neutropaenia, and liver dysfunction, headache and injection site reactions are described.[149]

The paradoxical development of MAS during treatment with inhibitors of the pro-inflammatory cytokines involved in its pathogenesis may be explained by concomitant infection as a trigger, since resolution of MAS with increased doses seemed to negate a causal relationship.[150]

4.5 T-cell inhibitor (Abatacept)

Mild infusion reactions may occur, but infectious risk does not appear to be increased, and neither does the risk of malignancy.[151]

4.6 JAK inhibitors

Like other DMARDs, JAK inhibitor use carries with it the increased risk of infection. The most frequent sites of infection are upper respiratory tract, urinary, and viral gastroenteritis. More severe and opportunistic infections were observed, such as tuberculosis (TB), fungal and Pneumocystis jirovecii pneumonia, however the overall infective risk does not seem to be significantly increased with appropriate pre-emptive management, compared to other established bDMARDs. A mild increase in transaminases, lipid profile derangement with increase in cholesterol levels and cytopaenias, are also reported.[84]

5. Non-pharmacological management

Holistic care of children with JIA requires multidisciplinary input and includes non-pharmacological management highlighted by ACR guidelines.[35] The non-pharmacological aspects include physical therapy and optimising joint function (physiotherapy and occupational therapy), screening for uveitis, monitoring for disease activity, adverse effects of medicines, exercise, growth and nutrition, vaccination status, support for mental and emotional health, supporting progress in school and transitional care into adulthood.

5.1 Vaccinations

Given the propensity for infections in children taking agents that have potent effects on the immune system, preventative measures such as vaccinations are critical.

Immunisations should occur as per the regional national immunisation schedule and windows of opportunity for the administration of live vaccines sought.

Recent guidelines for immunisations in children with rheumatic diseases suggest ways to navigate this important concern, including the immunisation of household contacts. Whether the antibody titres of children should be checked prior to the commencement of immunosuppressive

therapy is uncertain, although this may be a useful practice in regions where the overall population vaccination coverage is low.[35,142]

5.2 Growth and Nutrition

In surveys conducted in JIA populations, up to ⅔ of children had been tried on a restrictive diet, which were mostly gluten and milk-free. However, inconclusive results and poor nutrition in some children highlighted the dangers of a depleted diet. A healthy, balanced diet for all children, with consideration of age-appropriate nutritional requirements is therefore advocated. Restricted and exclusion diets have no place in the management of JIA.[152,153]

There is also no evidence to support the use of unregulated supplements and herbal formulations specifically to treat JIA e.g. curcumin, omegas, probiotics. Using complementary and alternative treatments in combination with conventional health care may be beneficial but may also be associated with a higher burden of care, including time, energy, costs and the risk of drug interactions.[154–157] Safety of these formulations is a real concern and transparency regarding their use is encouraged.[158]

5.3 Importance of exercise

Children with JIA are known to have decreased muscle strength, fitness and well-being compared to their healthy counterparts. Tailor made programs including weight bearing, resistance training and muscle strength training are effective and recommended in children with JIA. A cognitive

behavioural program Rheumates@work, an online and in-person based program, showed good acceptance and satisfaction of participants, with 93.8% completing the program successfully. The benefits of exercise, land and water-based, for children with JIA are well described in a randomised controlled trial and has been shown to improve not only musculoskeletal health but also levels of fatigue and mental health. Sustaining the effects of any exercise program requires ongoing commitment, which should be addressed by behavioural changes in addition to a physical program.[159–164]

Physiotherapy and occupational therapy are needed to improve strength, flexibility, range of motion, endurance, reverse functional deficits, prevent injury and improve activities of daily living including schooling and may also be instrumental in assisting with pain management. Mental health is undoubtedly affected by chronic pain, fatigue and concerns of disability further exacerbated by loss of school hours and social interaction with peers. Cognisance of the effect of chronic illness on patients and their families, with access to counselling and support is essential. The involvement of these health care professionals as part of the multidisciplinary team are essential in JIA care pathways.

5.4 Transitional care

Transition from paediatric to adult rheumatology care is an important aspect of the management of children and adolescents with chronic diseases such as JIA.[165] Studies describe increased morbidity and mortality during this vulnerable period, with few reporting reduced admission rates and a reduction in surgeries in those following transitional care programs.[166] Transition

should therefore be a planned process during which independence is facilitated, as care moves safely from a child-centred to a more adult approach. The transition plan should include the appropriate time for transition, and should be discussed with patients and their caregivers, with adequate preparation and management of expectations, to maintain continuity of care. Challenges to transitional care include lack of specific transitional care pathways, support during the process, lack of infrastructure, and transition driven by complex factors other than patient readiness.[167]

A consensus based international set of recommendations and standards for transitional care have been developed by the PreS/ EULAR taskforce[168], the Spanish Society of Paediatric Rheumatology[166] and NICE (UK).[169] In addition, adaptable transition programs (e.g. Ready Steady Go)[170] and tools to assist the transition process have been developed e.g. the ACR Transition Working Group toolkit[171] which includes patient readiness assessments prior to transfer as well as medical summary templates documenting pertinent information in an easily shared manner.

Adequate communication between patients, caregivers and the paediatric and adult rheumatology teams are an essential component of an effective transition program that ensures acceptable integration into adult services.[165,172–175]

6. Challenges

The challenges faced in the management of JIA are in many ways representative of concerns in musculoskeletal health care globally. The mandate of the Bone and Joint decade (2000-2010,

further extended to 2020), for consistently accessible care to improve the health-related quality of life for those with musculoskeletal disorders, have yet to be fully actualised. The sustainable development goals (SDG) for 2030 further include a clear objective to reduce inequity in all spheres. Furthermore, SDG Target 3.4 aims to reduce premature mortality from non-communicable diseases by a third through prevention and treatment, and to promote mental health and well-being. Succinctly reported by Briggs et al, an organised, global response to the inequities in musculoskeletal health care is needed for this ever increasing problem. The report argues that targets and monitoring for functional ability should be set as part of non-communicable diseases global health surveillance and the health SDG performance targets for 2030.[1]

This is particularly pertinent in JIA where maintenance of functional ability is paramount. While limited access to paediatric rheumatology care is not unique to low resourced countries, it is certainly exacerbated by broader socioeconomic issues and albeit appropriate prioritisation of immediate life-threatening communicable diseases over non-communicable diseases. Addressing the disparity in access to the 'right care' would support the statement by the global Task Force of paediatric rheumatologists that the goals of treatment of JIA are to control signs and symptoms, prevent structural damage, avoid comorbid conditions and drug toxicities; and to optimise function, growth and development, quality of life and social participation.[176,177] The need for urgent access to specialist care and medicines during the 'window of opportunity' where treatment is thought to be most effective, is emphasised in order to limit long-term joint damage, associated disability and its negative impact on quality of life. However, there are significant

issues with appropriate access in many countries and particularly in low-resource countries, which further contributes to the burden of disease and long-term disability.[178,179]

Moving forward, recognition of JIA and the guaranteed support of JIA management at policymaker level, plays an integral role in outcomes. The implementation of a government mandated universal access program for JIA in Chile, resulted in earlier access to a paediatric rheumatologist and JIA diagnosis, increased rates of treatment with biologic drugs, higher rates of clinical remission, and lower rates of uveitis complications. The success of the program underscores the importance of appropriate support and commitment towards care, in yielding positive outcomes.[180]

In another example, the Australian paediatric rheumatology community came together in an unprecedented way in 2021. Stakeholders voiced their concerns about the inadequacy of care and inability of the healthcare system to appropriately handle the current and ever growing population of children with JIA. By engaging with officials and policymakers, the resultant governmental inquiry recognised the limitations of its current healthcare system, and have made interim recommendations for capacity building to improve the management of childhood rheumatic diseases, a positive first step on the trajectory towards improved care.

Raising awareness, evaluating models of care, and facilitating training to enable the existing workforce to make a diagnosis of JIA and deliver care, are the focus of many collaborative initiatives,[176,181–184] which have assisted in the development or further expansion of many paediatric rheumatology services worldwide.[185–188] Where these services are limited or

unavailable in person, telemedicine and online training have enabled proper diagnosis and management, by up-skilling locally based medical professionals and caregivers to facilitate shared care.[189–192]

Challenges at local levels are acknowledged, which may include a limited workforce, as well as access and availability of medicines and facilities to optimise care. Cost is often a limiting factor in less resourced regions.

The 2022 Global Musculoskeletal Task Force survey reviewed some of these concerns, Appendix 2.[193] Respondents once again agreed on the medicines deemed necessary for inclusion on the WHO EML, in line with the previous survey[194] and cited lack of access to or availability of medicines as major barriers, rather than lack of a workforce. The medicines used in the management of JIA are summarised in Tables 8 and 9.[195-200] Availability of these medicines in paediatric doses would avoid wastage and ensure cost effectiveness.

The results of the survey are further expanded in the letter of response to the WHO EML committee's queries about the 2021 submissions for tocilizumab, anakinra and triamcinolone hexacetonide. (Appendix 3)

The growth of paediatric rheumatology around the world is gaining momentum. Having the necessary medicines available through the WHO EML will be an important step towards addressing this inequity and will enable treatment of many children with JIA, avoiding disability and ensuring a better quality of life.

Table 8: Summary of medicines used in the treatment of JIA

INN	ATC	Year of FDA/ EMA approval [1]	Mechanism of Action	Tablet/ formulation unit size	Drug Tariff price (£) [2]
Non-steroidal Anti-inflammatory drugs (NSAIDs)					
Ibuprofen	M01AE01	1986 (tablet) 1999 oral suspension	NSAIDs inhibit cyclooxygenase (COX) in the metabolism of arachidonic acid to prostaglandins, prostacyclins and thromboxanes.	400mg tablet 100mg/5mL oral suspension	4.9 (60) but cheaper OTC products available in the market 8.88 (500mL)
Naproxen	M01AE02	1993 (tablet) 1994 oral suspension	See above	250mg tablet 25mg/1mL	1.01 (28) 110 (100mL)
Acetylsalicylic acid	N02BA01	Before 1982	See above	300mg disp tablet	1.06 (32)
Corticosteroids					
Systemic					
Oral Prednisolone Prednisone	H02AB06 H02AB07	1982 tablet 2002 oral solution 2005	Corticosteroids bind to glucocorticoid receptors, which causes a conformational change in the receptor. The receptor-glucocorticoid complex can move into the cell nucleus, where it dimerizes and binds to glucocorticoid response elements. Glucocorticoid response elements are associated with genes that either suppress or stimulate transcription, which results in ribonucleic acid and protein synthesis; Ultimately, these agents inhibit transcription factors that control synthesis of pro-inflammatory mediators, including macrophages, eosinophils, lymphocytes, mast cells, and dendritic cells. Another important effect is inhibition of phospholipase A2, which is responsible for production of numerous inflammatory mediators. Corticosteroids inhibit genes responsible for expression of cyclooxygenase-2, inducible nitric oxide synthase, and pro-	5mg tablet 10mg/1mL Not available in UK	0.79 (28) 55.5 (30mL)

			inflammatory cytokines, including tumor necrosis factor alpha and various interleukins. In contrast, corticosteroids initiate upregulation of lipocortin and of annexin A1, a protein that reduces prostaglandin and leukotriene synthesis and that also inhibits cyclooxygenase-2 activity and reduces neutrophil migration to inflammatory sites		
Intravenous Methylprednisolone	H02AB04	2004	See above	1g strength	17.30 (1 vial)
Intra-articular					
Triamcinolone hexacetonide	H02AB08	1982	See above	Currently unavailable in the UK- imported products >40.0 per vial	Previous price: 120.00 for 10 vials (20mg/1mL)
Triamcinolone acetonide	H02AB08	1982	See above	40mg/1mL	7.45 (5 vials)
Depo Methyl prednisolone	H02AB04	1982	See above	80mg/2mL preparation	6.18 (1 vial)
Topical					
Prednisolone eye drops	S01BA04	1994	See above	per 5ml dropper (1%)	1.82
Conventional synthetic DMARDs					
Methotrexate	L04AX03	1994 tablet 2007 oral solution 2013 SC	Methotrexate, is a folic acid analogue and a potent competitive inhibitor of many enzymes in the folate pathway	2.5mg tabs 2mg/1mL oral solution SC (different strengths)	1.88 (28) 125 (65mL) 12.87 (7.5mg) up to 16.56 (30mg)
Leflunomide	L04AA13	2005	Leflunomide is an isoxazole derivative that is rapidly absorbed from the GI tract and has an immunomodulatory effect mainly by inhibiting pyramidine synthesis	10mg tablets	2.51 (30)

Sulfasalazine	A07EC01	2002 Before 1982 (oral suspension)	Sulfasalazine is a prodrug, which bacterial enzymes in the colon convert into the active components, sulphapyridine and 5-aminosalicylic acid	500mg tablets 250mg/5mL	32.85 (112) 94.22 (500mL)
Chloroquine and Hydroxychloroquine	P01BA01	2003 1994 (hydroxychloroquine)	Chloroquine and hydroxychloroquine increase pH within intracellular vacuoles and alter processes such as protein degradation by acidic hydrolases in the lysosome, assembly of macromolecules in the endosomes, and post translation modification of proteins in the Golgi apparatus. The antirheumatic properties of these compounds results from their interference with "antigen processing" in macrophages and other antigen-presenting cells. Acidic cytoplasmic compartments are required for the antigenic protein to be digested and for the peptides to assemble with the alpha and beta chains of MHC class II proteins. As a result, antimalarials diminish the formation of peptide-MHC protein complexes required to stimulate CD4+ T cells and result in down-regulation of the immune response against autoantigenic peptides	250mg tablets 200mg tablets	8.59 (20) 3.21 (60)
Ciclosporine A	L04AD01	1995 2001 oral solution	Cicosporin A is a cyclic peptide of fungal origin and has an immuno- modulatory effect by inhibiting the calcium-dependent and calmodulin-dependent serine/threonine protein phosphatase calcineurin. It is shown to inhibit the production of several interleukins	25mg capsules 100mg/1mL	18.37 (30) 164.7 (50mL)
Biologic DMARDs					
Tumour necrosis Factor inhibitors					
Etanercept	L04AB01	Originator 1998 FDA/ 2000 EMA	Etanercept is a TNF (tumour necrosis factor)- α inhibitor; it blocks the TNF alpha receptor and renders it inactive. TNF alpha is one of the cytokines which takes part in the inflammatory/immune cascade, and is present in high numbers in arthritic processes (both in plasma and inflamed tissues such as synovial liquid, bursae, etc)	Enbrel 25mg powder and solvent Enbrel 10mg paediatric vial	357.5 (4 vials) 143 (4 vials)

		Biosimilar 2016 FDA/ 2016 EMA	The inhibition of TNF-α is competitive in nature. Due to etanercept pharmacokinetics, twice a week dosing is recommended for better effect if needed	Benepali (biosimilar) 25mg PFS	357.5 (4)
Infliximab	L04AB02	Originator 1998 FDA/ 1999 EMA Biosimilar 2016 FDA/ 2013 EMA	Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-α. Infliximab is therefore effective in those conditions where there are elevated levels of TNF-α	Remicade 100mg Remsima 100mg (biosimilar)	419.62 (1) 377.66 (1)
Adalimumab	L04AB04	Originator 2002 FDA/ 2003 EMA Biosimilar 2016 FDA/ 2017 EMA	Adalimumab is a monoclonal antibody that binds to TNF-α, renders it inactive by preventing binding with its receptors and exerting its actions. The amount of TNF "inactivated" is higher than with etanercept and this leads to a prolonged action and allows for fortnightly dosing. Adalimumab also affects the immunological and inflammation cascade as TNF-α is one of the main cytokines involved in inflammatory response. These regulatory effects have been shown to lead to radiological improvement in rheumatology patients	Humira 40mg PFS Humira 20mg PFS Amgevita (biosimilar) 40mg PFS Amgevita 20mg PFS	704.28 (2) 352.14 (2) 633.6 (2) 154 (1)
Golimumab	L04AB06	2009 FDA/ 2009 EMA	Golimumab is a human monoclonal antibody that forms high affinity, stable complexes with both the soluble and transmembrane bioactive forms of human TNF-α, which prevents the binding of 50TNF-α to its receptors.	100mg PFS 50mg PFS	1525.94 (1) 762.97 (1)
IL-6 inhibitor					
Tocilizumab	L04AC07	Intravenous 2010 FDA/ 2009 EMA	Tocilizumab is a fully human anti-IL-6 receptor monoclonal antibody. Tocilizumab inhibits the function of the cytokine IL-6 by preventing the association of IL-6 with the IL-6 receptor (IL-	IV 400mg vial	512.00 (1)

		SC 2013	6R), in the circulation in its soluble form, as well as on the cell surface	SC 162mg PFS	913.12 (4)
T-cell inhibitor					
Abatacept	L04AA24	IV and SC 2005 FDA/ 2007 EMA	Abatacept selectively modulates a key costimulatory signal required for full activation of T lymphocytes expressing CD28. Full activation of T lymphocytes requires two signals provided by antigen presenting cells: recognition of a specific antigen by a T cell receptor (signal 1) and a second, costimulatory signal. A major costimulatory pathway involves the binding of CD80 and CD86 molecules on the surface of antigen presenting cells to the CD28 receptor on T lymphocytes (signal 2). Abatacept selectively inhibits this costimulatory pathway by specifically binding to CD80 and CD86. Studies indicate that naive T lymphocyte responses are more affected by abatacept than memory T lymphocyte responses	IV: 250mg IV vial SC: 125mg PFS Prices for 50mg and 87.5mg PFS not available	302.4 (1) 1209.6 (4)
IL-1 inhibitor					
Anakinra	L04AC03	2001 FDA/ 2002 EMA	Anakinra is an Interleukin inhibitor which neutralises the biologic activity of interleukin-1α and interleukin-1β. Anakinra blocks the IL-1 signalling pathway thereby inhibiting pro-inflammatory effects Since the antagonism is competitive in nature and the half live is short, anakinra needs to be administered daily	100mg PFS:	183.61 (7)
Canakinumab	L04AC08	2009 FDA/ 2009 EMA	Canakinumab is a human monoclonal anti-human interleukin-1 beta (IL-1 beta) antibody of the IgG1 kappa isotype. It binds specifically to human IL-1 beta and neutralises the biological activity of human IL-1 beta by blocking its interaction with IL-1 receptors, thereby preventing IL-1 beta-induced gene activation and the production of inflammatory mediators	150mg injection	9927.8 (1)
Rilonacept	L04AC04	2008 FDA/ 2009 EMA (withdrawn from use in EMA)	Rilonacept blocks IL-1β signaling by acting as a soluble decoy receptor that binds IL-1β and prevents its interaction with cell surface receptors. Rilonacept also binds IL-1α and IL-1 receptor antagonist (IL-1ra) with reduced affinity. The equilibrium dissociation constants for rilonacept	Not available in UK	-

			binding to IL-1β, IL-1α and IL-1ra were 0.5 pM, 1.4 pM and 6.1 pM, respectively.		
IL 17A inhibitor					
Secukinumab	L04AC10	2015 FDA/ 2015 EMA 2022 EMA (paediatric indications)	IL-17 blocker Secukinumab is a fully human IgG1/κ monoclonal antibody that selectively binds to and neutralises the proinflammatory cytokine interleukin-17A (IL-17A). Secukinumab works by targeting IL-17A and inhibiting its interaction with the IL-17 receptor, which is expressed on various cell types including keratinocytes. As a result, secukinumab inhibits the release of proinflammatory cytokines, chemokines and mediators of tissue damage and reduces IL-17A-mediated contributions to autoimmune and inflammatory diseases	150mg PFS 75mg PFS	1218.78 (2) 304.7 (1)
IL12/23 inhibitor					
Ustekinumab	L04AC05	2009 FDA/ 2009 EMA	Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with specificity to the shared p40 protein subunit of human cytokines interleukin (IL)-12 and IL-23. Ustekinumab inhibits the bioactivity of human IL-12 and IL-23 by preventing p40 from binding to the IL-12Rβ1 receptor protein expressed on the surface of immune cells. Ustekinumab cannot bind to IL-12 or IL-23 that is already bound to IL-12Rβ1 cell surface receptors. Thus, ustekinumab is not likely to contribute to complement- or antibody-mediated cytotoxicity of cells with IL-12 and/or IL-23	45mg	PFS or paediatric vial 2147 (1)
CD20 inhibitor					
Rituximab	L01FA01	Originator 1997 FDA/ 1998 EMA Biosimilar 2018 FDA/ 2017 EMA	Rituximab is a chimeric (murine / human) monoclonal antibody directed against B cells. Treatment is aimed at reducing autoantibody production, and thereby disease activity. Rituximab spares B cell progenitors, and B cells usually repopulate 4-12 months after therapy. CD27+ B-cells (memory B-cells) can remain suppressed for 2 years after depletion	MAbThera 500mg vial Truxima (biosimilar) 500mg vial	873.15 (1) 785.84 (1)
Targeted synthetic DMARDs					
Janus Kinase inhibitors					

Tofacitinib	L04AA29	2012 FDA/ 2017 EMA Oral solution. 2020 FDA/ 2021 EMA	Selective inhibitor of the JAK family (JAK1, JAK2, JAK3 and to a lesser extent TyK2). This attenuates signalling of IL (2, 4, 6, 7, 9, 15 and 21) and type I and II interferons	5mg tablets Liquid: price not yet published	690.03 (56)
Baricitinib	L04AA37	2019 FDA/ 2017 EMA	Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, Tyrosine Kinase 2 and JAK3 with IC50 values of 5.9, 5.7, 53 and > 400 nM, respectively. Janus kinases (JAKs) are enzymes that transduce intracellular signals from cell surface receptors for several cytokines and growth factors involved in haematopoiesis, inflammation, and immune function. Within the intracellular signalling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription (STATs), which activate gene expression within the cell. Baricitinib modulates these signalling pathways by partially inhibiting JAK1 and JAK2 enzymatic activity, thereby reducing the phosphorylation and activation of STATs.	2mg and 4mg tablets	805.56 (28)

Table 9: bDMARDs Cost Estimation for JIA

Drug	Unit cost (£) per vial/syringe	Dose	Dose 10kg child	Annual cost (£) 10kg child	Dose 50kg child	Annual cost (£) 50kg child
Anakinra (SOJIA)	26.23 per 100mg PFS	2-8mg/kg OD Off-label up to 12mg/kg OD	20-80mg OD 120mg OD	9 573.95 19 147.9	100-400mg OD 400mg OD (ceiling dose)	9 573.95-38295.8 38 295.8
Canakinumab (SOJIA) [4]	9927.8 per 150mg vial	4mg/kg Q4W	40mg Q4W	119 133.6	200mg Q4W	238 267.2
Tocilizumab IV [3]	512.00 per 400mg vial Or 256.00 per 200mg vial	**SOJIA** <30kg: 12mg/kg **JIA** 10mg/kg Q4W	120mg Q2W 100mg Q4W	6 656 3 072	**SOJIA** 8mg/kg 400mg Q2W **JIA** 8mg/kg Q4W 400mg Q4W	13 312 6 144
Tocilizumab SC	228.28 per 162mg PFS		**SOJIA** 162mg Q2W **JIA** 162mg Q3W	5 935.28 3 880.76	**SOJIA** 162mg Q1W **JIA** 162mg Q2W	11 870.56 5 935.28
Etanercept originator	35.75 per 10mg vial	0.4mg/kg TW	4mg TW	3 718	NA	NA
Etanercept biosimilar	89.38 per 25mg PFS		NA	NA	25mg TW (rounded)	9 295.52
Adalimumab originator	176.07 per 20mg PFS 352.14 per 40mg PFS	<30kg 20mg Q2W >30kg 40mg Q2W	20mg Q2W	4577.82	40mg Q2W	9 155.64
Adalimumab biosimilar	154 per 20mg PFS 316.8 per 40mg PFS		20mg Q2W NA	4004 NA	NA 40mg Q2W	NA 8 236.8
Infliximab originator [3]	419.62 per 100mg vial	6-12mg/kg	60mg Q4W	13 doses incl LD: 5 455.06	300mg Q4W	13 doses incl LD: 15 525.94
Infliximab biosimilar [3]	377.66 per 100mg vial		60mg Q4W	13 doses incl LD: 4909.58	300mg Q4W	13 doses incl LD: 14 728.74
Golimumab	762.97 per 50mg PFS 1525.94 per 100mg PFS	30mg/m^2 Q4W	10kg=0.49m2 14.7mg Q4W	NA Paediatric vial not available in the UK	50mg Q4W	9 155.64
Abatacept IV [3]	302.4 per 250mg vial	10mg/kg Q4W	100mg Q4W	14 doses incl LD: 4 233.6	500mg Q4W	14 doses incl LD: 8 467.2
Abatacept SC	302.4 per 125mg PFS		50mg Q1W	Price not available for 50mg PFS	125mg Q1W	3 628.8

Secukinumab	304.7 per 75mg PFS 609.39 per 150mg PFS	< 50kg - 75mg Q4W >50kg 150mg/kg Q4W	75mg Q4W	16 doses incl LD: 4 875.2	150mg Q4W	16 doses incl LD: 9 750.24
Ustekinumab	2147 per 45mg PFS or paediatric vial	0.75mg/kg Q12W	7.5mg Q12W	5 doses incl LD: 1 0735	37.5mg Q12W	5 doses incl LD: 1 0735
Tofacitinib	12.32 per 5mg tablet	10-20kg 3.2mg po BD	NA- liquid only licensed for 2 years and over	Price not available for liquid product	5mg BD	8993.6
Baricitinib	31.18 per 2mg OR 4mg tablet	-	NA paediatric doses for JIA not available	NA, paediatric doses for JIA not available	Off-label from RA 4mg OD	11 380.7
Rituximab originator [3]	873.15 per 500mg vial	750mg/m^2 X 2 doses two weeks apart, 6 monthly	2 cycles 10kg=0.49m2 400mg (rounded) x 4 doses	3 492.6	2 cycles 50kg=1.5m2 1000mg (capped) x 4 doses	6 985.2
Rituximab biosimilar [3]	785.84 per 500mg vial		4 doses of 750mg/m2 per year (2 cycles) 10kg=0.49m2 400mg (rounded) x 4 doses	3 142.36	4 doses of 750mg/m2 per year (2 cycles) 50kg=01.5m2 1000mg (capped) x 4 doses	6 286.72

Table 10: csDMARDs Cost Estimation for JIA

Drug	Unit cost (£) per vial/syringe	Dose 10kg child	Annual cost (£) 10kg child	Dose 50kg child	Annual cost (£) 50kg child
Methotrexate (tablets)	0.07 per 2.5mg tablet	10-15mg/m2 10kg=0.49m2 7.5mg Q1W	10.92	10-15mg/m2 50kg=1.5m2 22.5mg Q1W	32.76
Methotrexate (liquid) [5]	1.92 per 1mg liquid	10-15mg/m2 10kg=0.49m2 7.5mg Q1W	748.8	10-15mg/m2 50kg=1.5m2 22.5mg Q1W	2246.4
Methotrexate (SC)	12.87 (7.5mg) up to 16.56 (30mg) per 1 pen	10-15mg/m2 10kg=0.49m2 7.5mg Q1W	per pen 12.87 =669.24	10-15mg/m2 50kg=1.5m2 22.5mg Q1W	per pen 16.11 = 837.72
Leflunomide (tablets)	0.08 per 10mg tablet	NA	NA	20mg OD	29.08

[1] EMA approval dates only given for biological medicines. DMARDs and other supportive medicines' approval dates different in the EU depending on the member country

[2] Cost of PEN devices is the same as Pre-filled syringes (PFS) of the same strength (where available)

[3] Prices quoted do not include manufacturing of the product under aseptic conditions and extra ancillaries (giving sets, bags, diluents, pre-medications) needed for administration. In centres with aseptic production units, vial sharing could lead to increased cost effectiveness, however affecting the licensing of the product (would render it unlicensed)

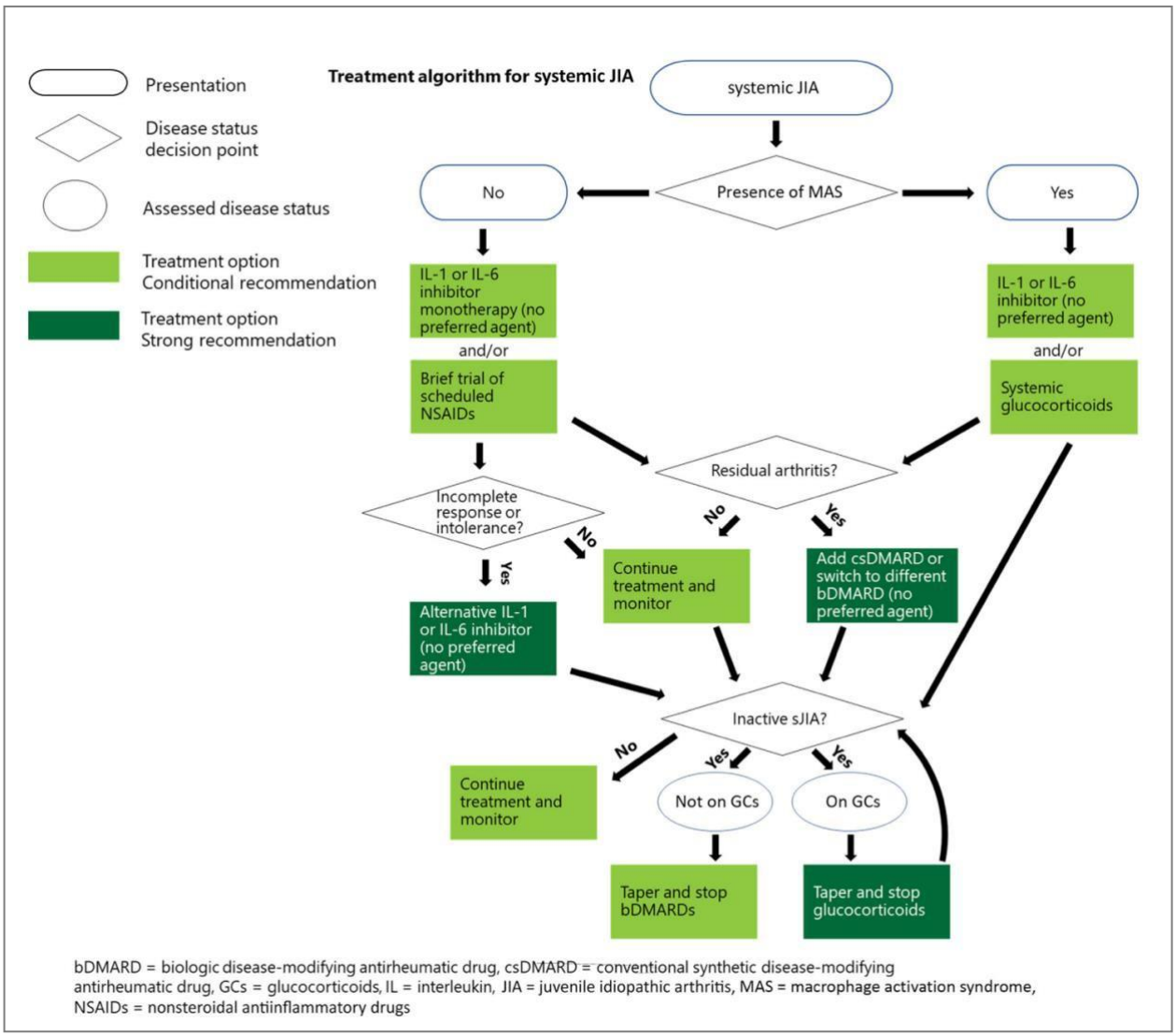
Prices do not take into consideration potential wastage occurring from expiry of the product once opened- real cost could be greater depending on dispensing services available

[4] Canakinumab could be made more cost effective by vial sharing in aseptic production units or by cohorting patients in day-case clinics. This would affect the licensing of the product (would render it unlicensed)
Rilonacept and Baricitinib are not yet approved for SOJIA or other subtypes of JIA
LD – loading dose

Appendix 1: Flow Charts of the Management of Juvenile Idiopathic Arthritis (JIA)

A. Systemic Onset JIA

Fig. 1 ACR[35] Therapeutic approach (2021)



bDMARD = biologic disease-modifying antirheumatic drug, csDMARD = conventional synthetic disease-modifying antirheumatic drug, GCs = glucocorticoids, IL = interleukin, JIA = juvenile idiopathic arthritis, MAS = macrophage activation syndrome, NSAIDs = nonsteroidal antiinflammatory drugs

Fig. 2(a) CARRA[201] Consensus Treatment Plans (2012): Glucocorticoid

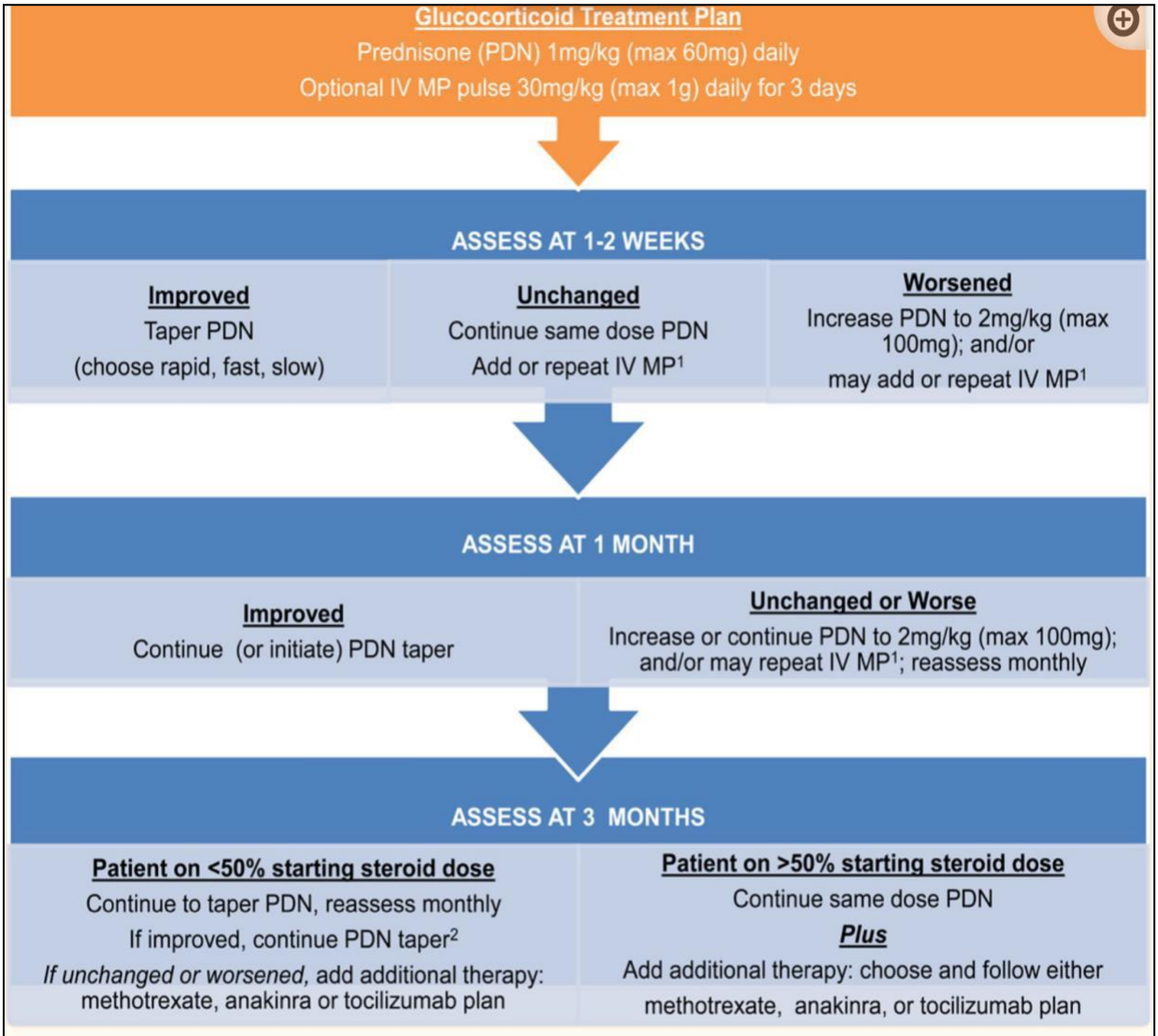


Figure 1

Glucocorticoid treatment plan. Note: [1]Intravenous methylprednisolone (IV MP) pulses are one dose weekly. [2]Patients who started with rapid taper may be off prednisone.

Fig. 2(b) CARRA[201] Consensus Treatment Plans (2012): Methotrexate

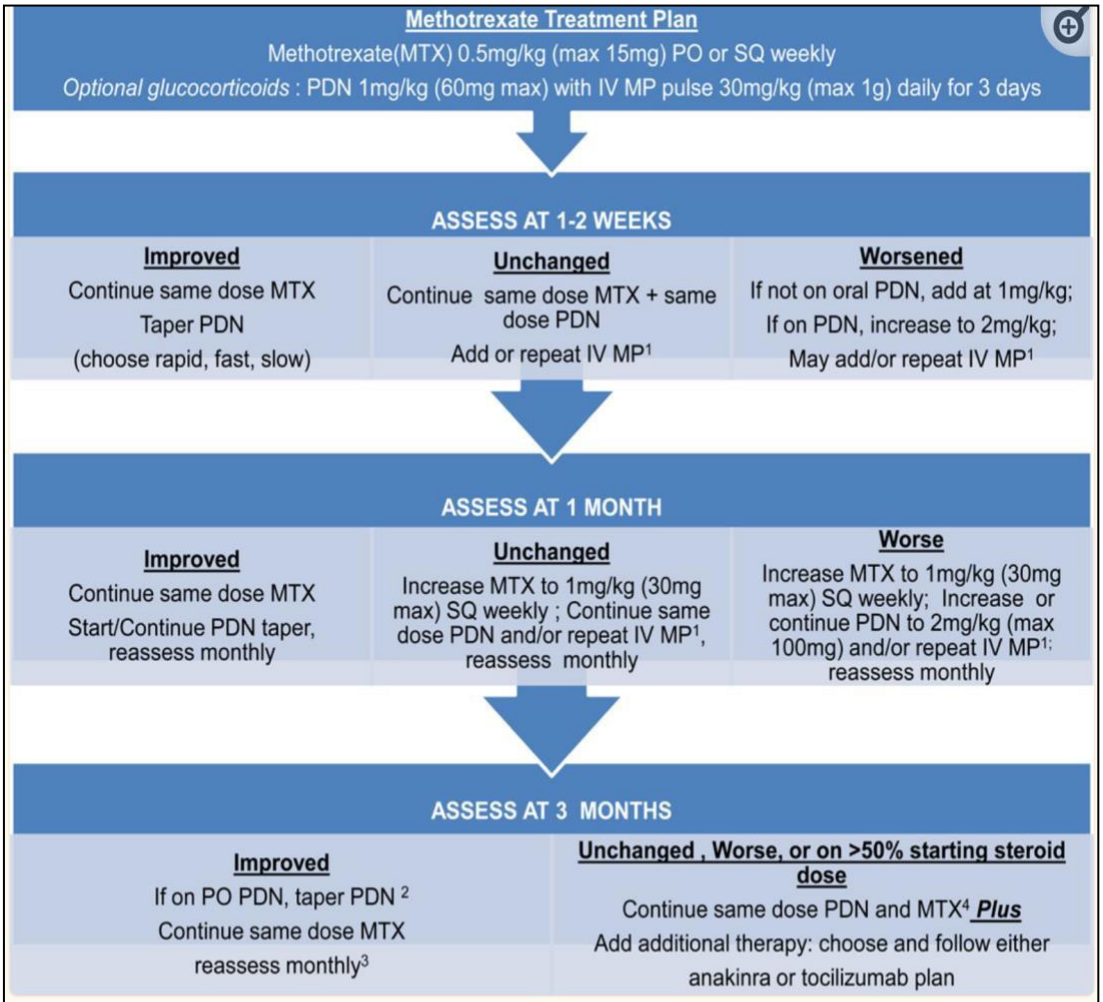


Figure 2

Methotrexate treatment plan. Notes: [1]Intravenous methylprednisolone (IV MP) pulses are one dose weekly. [2]Patients who started with rapid taper may be off prednisone. [3]If condition worsens follow "Unchanged, Worse" pathway. [4]If patient is intolerant of methotrexate, discontinue and add additional therapy.

Fig. 2(c) CARRA[201] Consensus Treatment Plans (2012): Anakinra

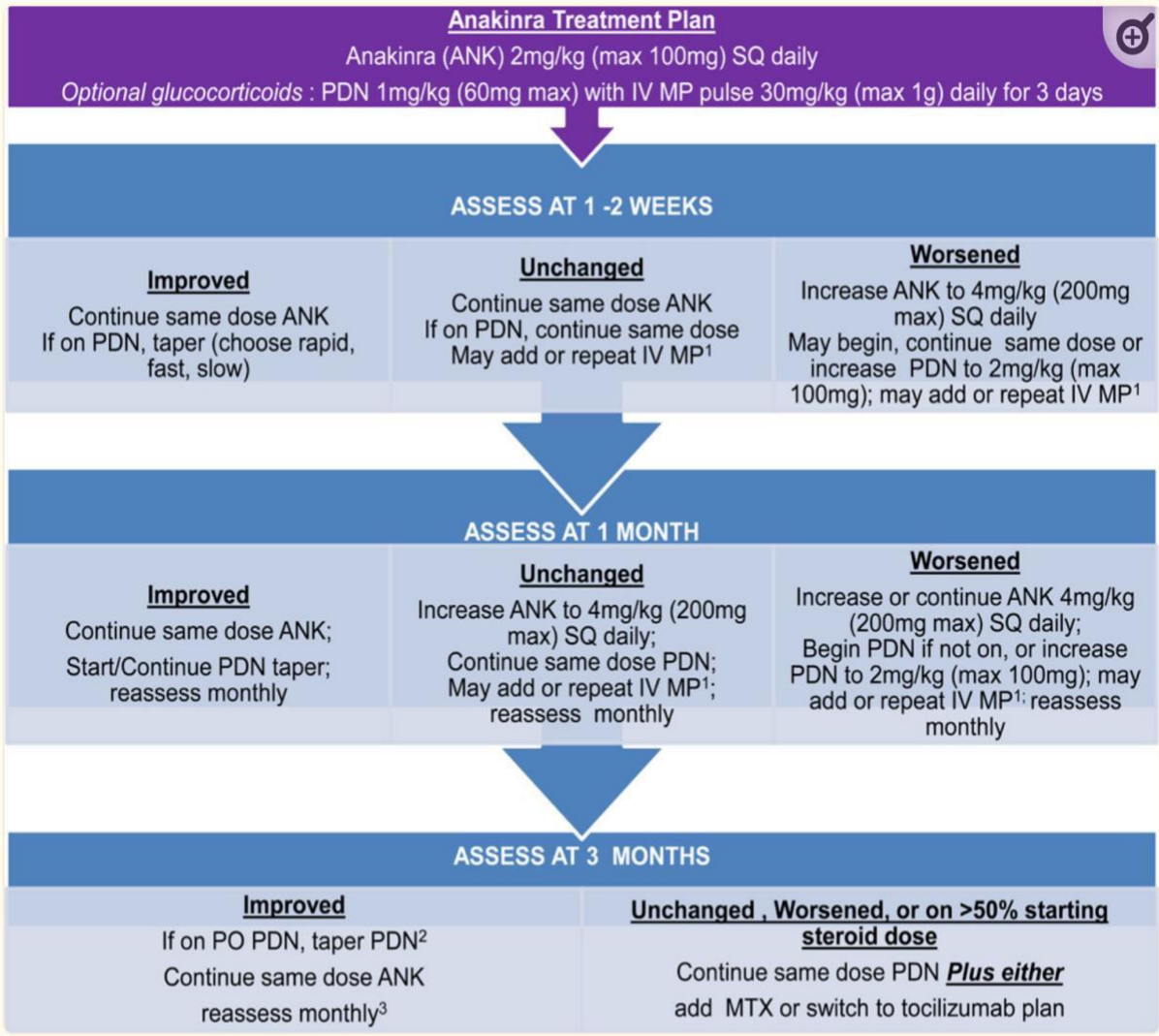


Figure 3

Anakinra treatment plan. Notes: [1]Intravenous methylprednisolone (IV MP) pulses are one dose weekly. [2]Patients who started with rapid taper may be off prednisone. [3]If condition worsens or patient is intolerant of anakinra follow "Unchanged, Worse" pathway.

Fig. 2(d) CARRA[201] Consensus Treatment Plans (2012):Tocilizumab

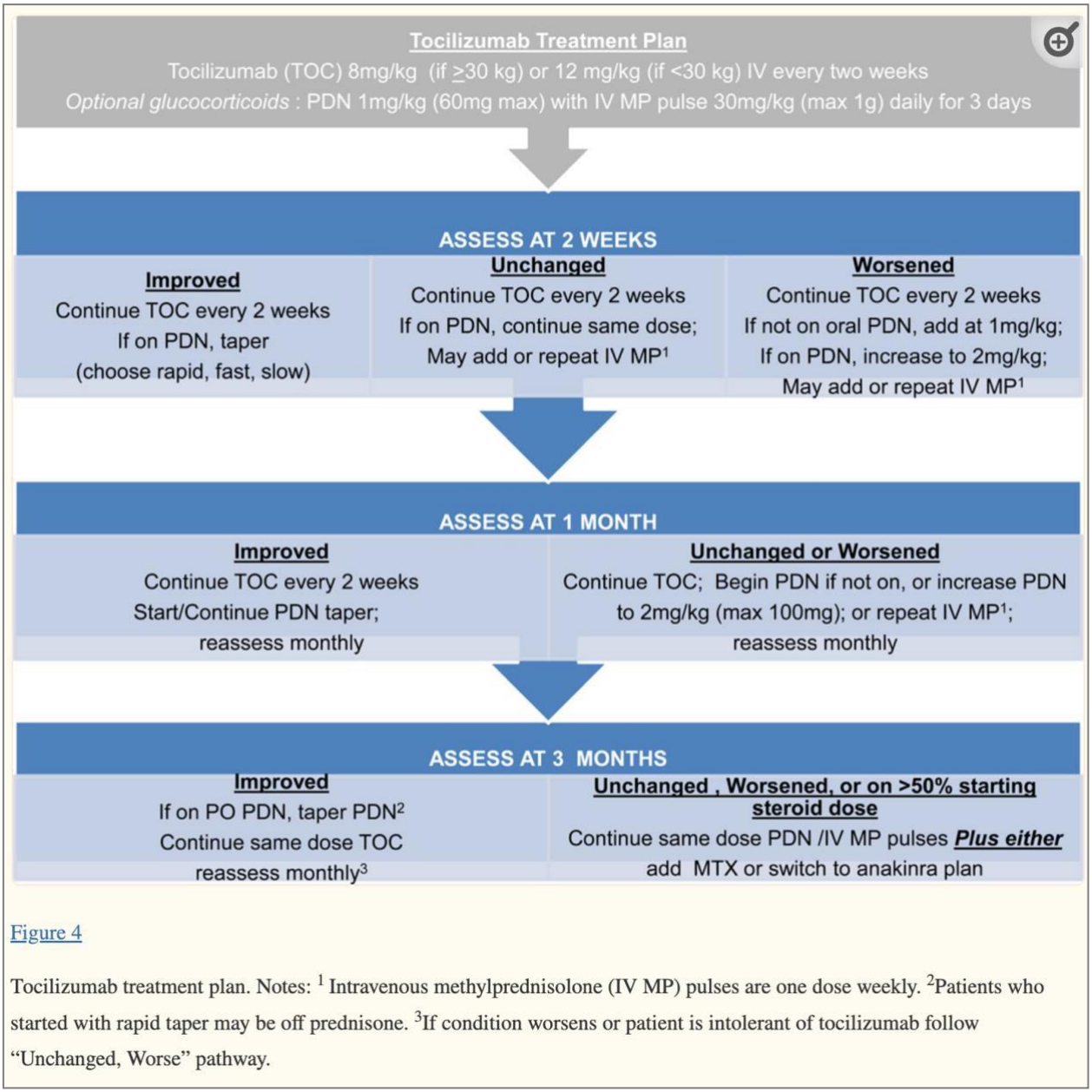
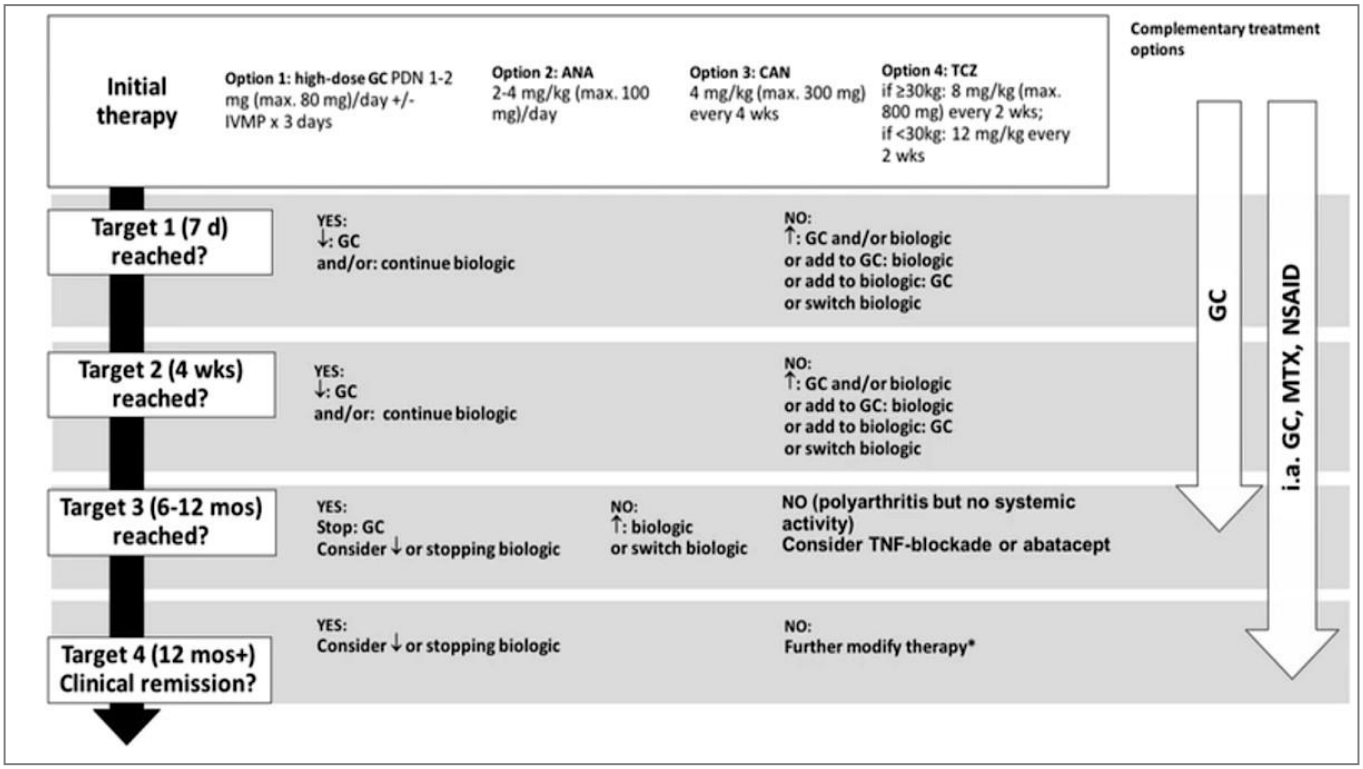


Figure 4

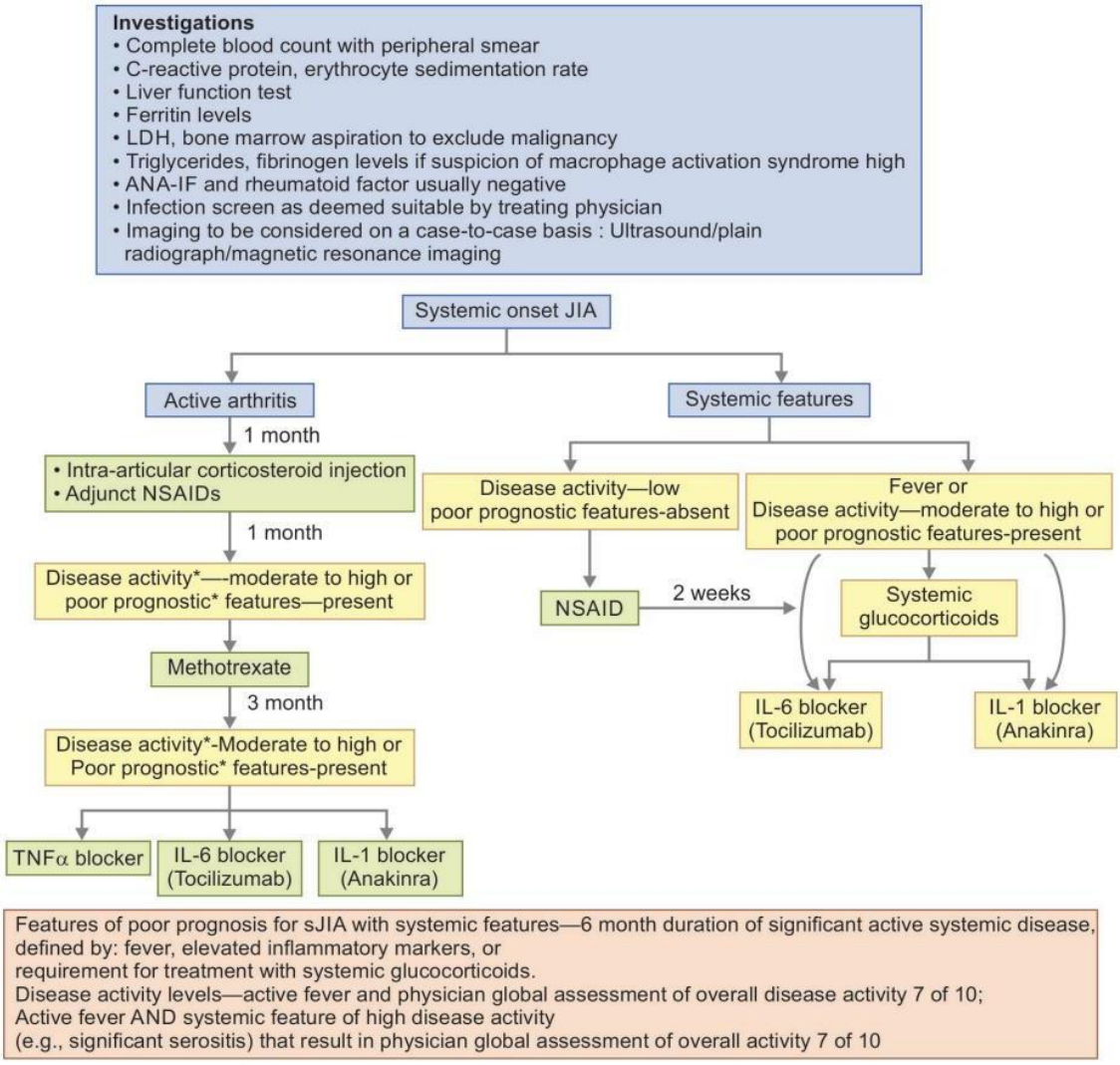
Tocilizumab treatment plan. Notes: [1] Intravenous methylprednisolone (IV MP) pulses are one dose weekly. [2]Patients who started with rapid taper may be off prednisone. [3]If condition worsens or patient is intolerant of tocilizumab follow "Unchanged, Worse" pathway.

Fig. 3 German[43] Treat-to-target consensus-based guidelines (2018)



Treat-to-target consensus treatment strategy for definitive SJIA. Maximal doses for glucocorticoids: i.v. methylprednisolone pulse therapy (20–30 mg/kg/day [max. 1000 mg/day) for 5 days or prednisolone equivalent 1–2 mg/kg/day (max. 80 mg/day). "Biologic" refers to anakinra, canakinumab or tocilizumab. Maximal doses for biologics: anakinra 8 mg/kg/day (max. 300 mg/days), canakinumab 8 mg/kg (max. 600 mg) every 4 weeks, tocilizumab (for body weight > 30 kg) 8 mg/kg (max. 800 mg) i.v. every 2 weeks and (for body weight < 30 kg) 12 mg/kg every 2 weeks. In addition, non-steroidal anti-inflammatory drugs may be used for symptom relief throughout. Abbreviations: ANA, anakinra; CAN, canakinumab; CID, clinical inactive disease; GC, glucocorticoids; i.a., intraarticular; IVMP, intravenous methylprednisolone pulse; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; PDN, prednisone/prednisolone equivalent; TCZ, tocilizumab; TNF, tumor necrosis factor-alpha. ↓ = decrease dose or frequency (taper); ↑ = increase dose or frequency

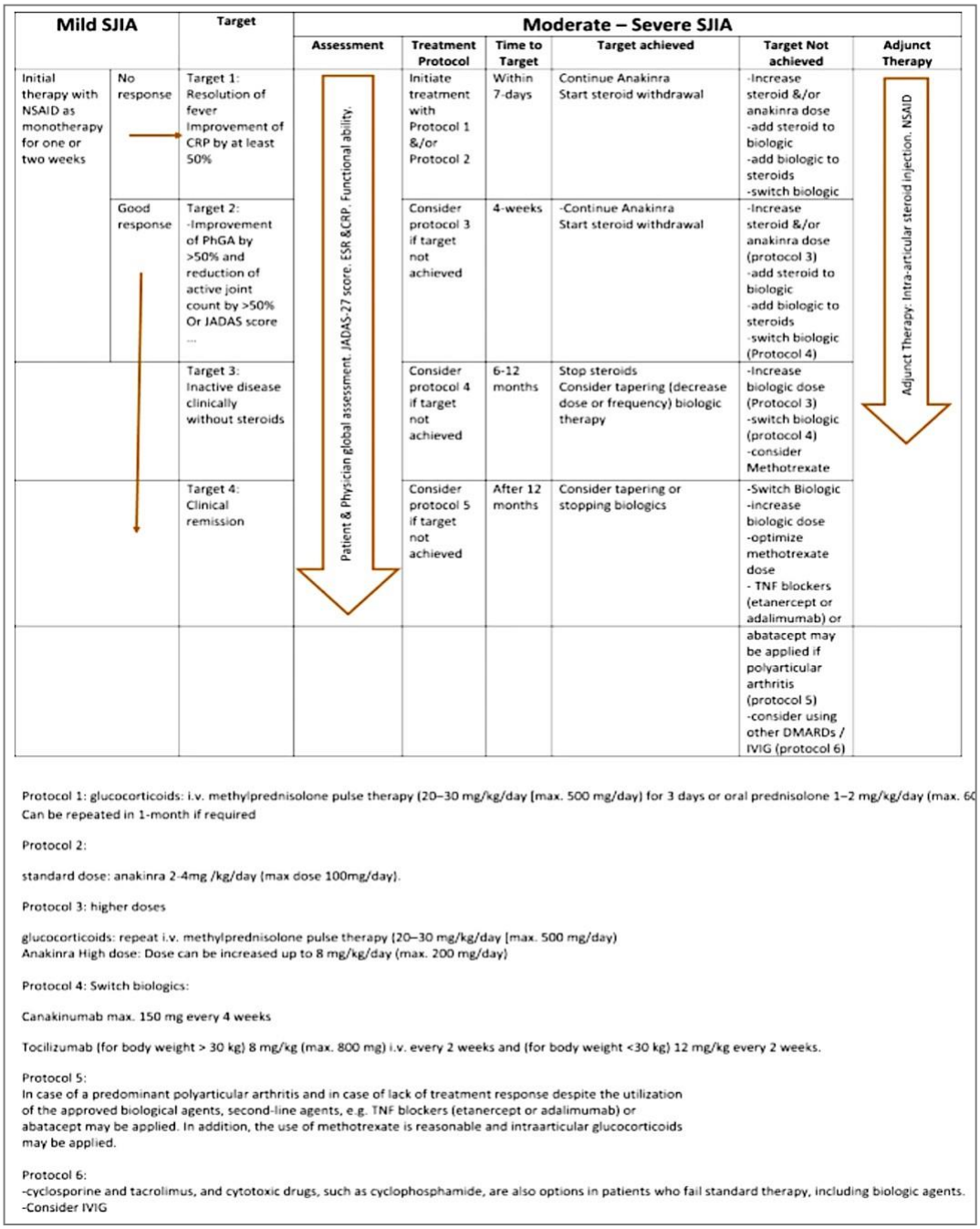
Flowchart 3: Management of systemic arthritis.



(ANA: antinuclear antibody; IF: immunofluorescence; IL: interleukin; JIA: juvenile idiopathic arthritis; LDH: lactate dehydrogenase; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF: tumor necrosis factor)

Fig. 4 Indian Academy of Paediatrics[207] (2022)

Fig. 5 Egyptian College of Paediatric Rheumatology[202] treat-to-target guidelines (2022)



Mild SJIA		Target	Moderate – Severe SJIA					
			Assessment	Treatment Protocol	Time to Target	Target achieved	Target Not achieved	Adjunct Therapy
Initial therapy with NSAID as monotherapy for one or two weeks	No response	Target 1: Resolution of fever Improvement of CRP by at least 50%	Patient & Physician global assessment. JADAS-27 score. ESR &CRP. Functional ability.	Initiate treatment with Protocol 1 &/or Protocol 2	Within 7-days	Continue Anakinra Start steroid withdrawal	-Increase steroid &/or anakinra dose -add steroid to biologic -add biologic to steroids -switch biologic	Adjunct Therapy: Intra-articular steroid injection. NSAID
	Good response	Target 2: -Improvement of PhGA by >50% and reduction of active joint count by >50% Or JADAS score ...		Consider protocol 3 if target not achieved	4-weeks	-Continue Anakinra Start steroid withdrawal	-Increase steroid &/or anakinra dose (protocol 3) -add steroid to biologic -add biologic to steroids -switch biologic (Protocol 4)	
		Target 3: Inactive disease clinically without steroids		Consider protocol 4 if target not achieved	6-12 months	Stop steroids Consider tapering (decrease dose or frequency) biologic therapy	-Increase biologic dose (Protocol 3) -switch biologic (protocol 4) -consider Methotrexate	
		Target 4: Clinical remission		Consider protocol 5 if target not achieved	After 12 months	Consider tapering or stopping biologics	-Switch Biologic -increase biologic dose -optimize methotrexate dose - TNF blockers (etanercept or adalimumab) or	
							abatacept may be applied if polyarticular arthritis (protocol 5) -consider using other DMARDs / IVIG (protocol 6)	

Protocol 1: glucocorticoids: i.v. methylprednisolone pulse therapy (20–30 mg/kg/day (max. 500 mg/day) for 3 days or oral prednisolone 1–2 mg/kg/day (max. 60
Can be repeated in 1-month if required

Protocol 2:

standard dose: anakinra 2-4mg /kg/day (max dose 100mg/day).

Protocol 3: higher doses

glucocorticoids: repeat i.v. methylprednisolone pulse therapy (20–30 mg/kg/day (max. 500 mg/day)
Anakinra High dose: Dose can be increased up to 8 mg/kg/day (max. 200 mg/day)

Protocol 4: Switch biologics:

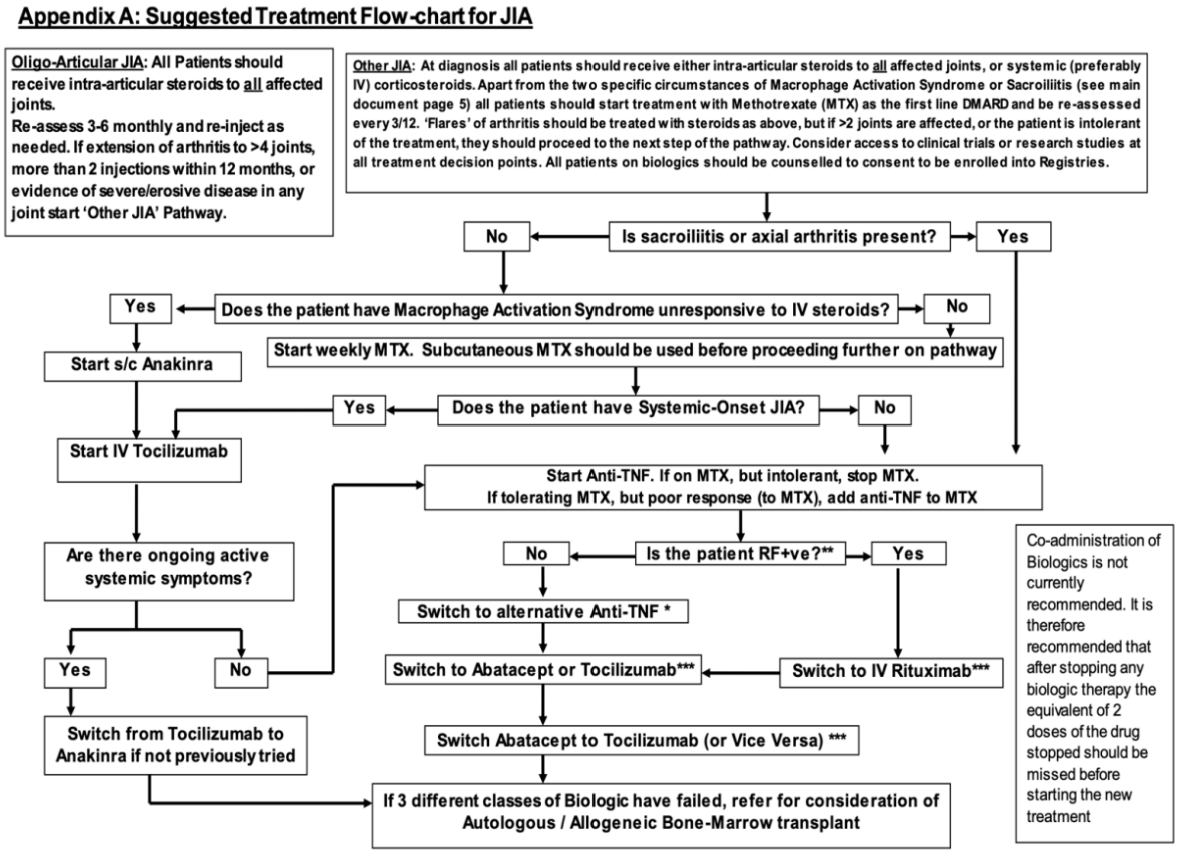
Canakinumab max. 150 mg every 4 weeks

Tocilizumab (for body weight > 30 kg) 8 mg/kg (max. 800 mg) i.v. every 2 weeks and (for body weight <30 kg) 12 mg/kg every 2 weeks.

Protocol 5:
In case of a predominant polyarticular arthritis and in case of lack of treatment response despite the utilization of the approved biological agents, second-line agents, e.g. TNF blockers (etanercept or adalimumab) or abatacept may be applied. In addition, the use of methotrexate is reasonable and intraarticular glucocorticoids may be applied.

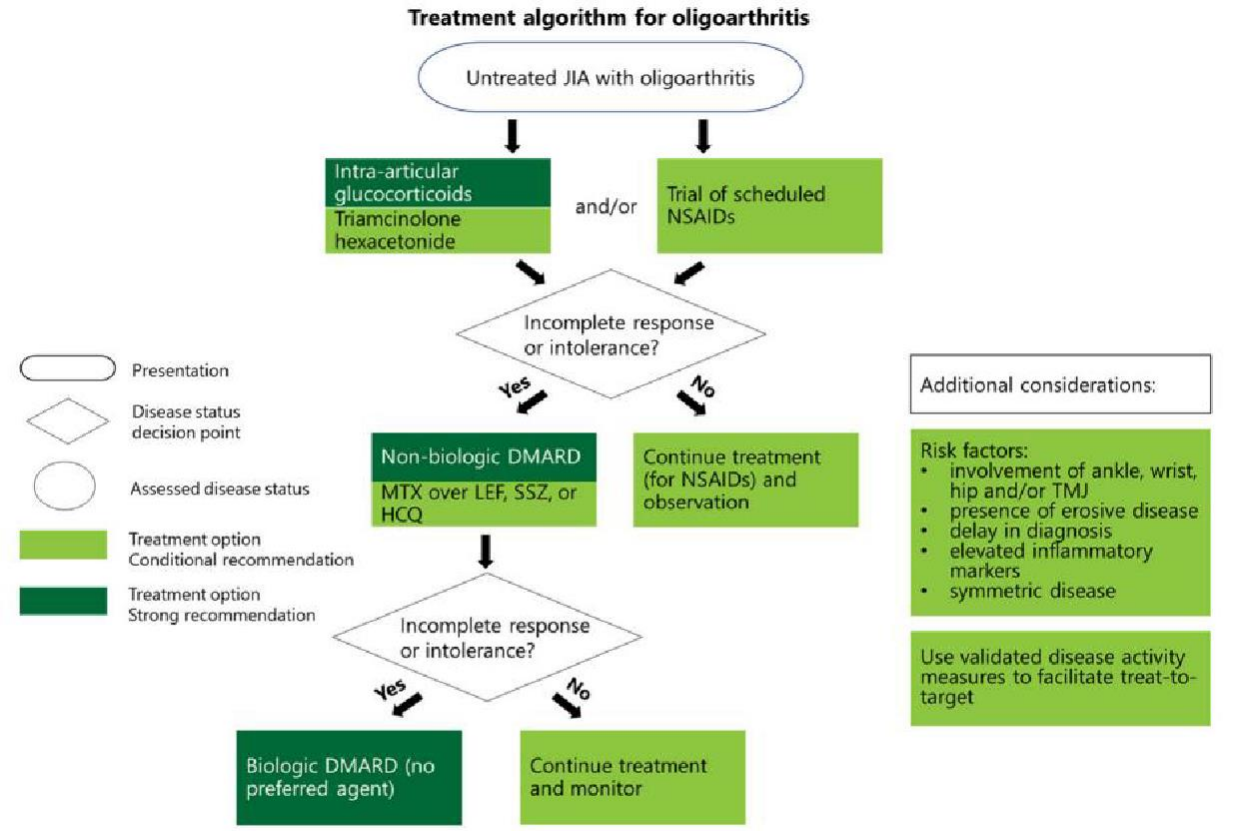
Protocol 6:
-cyclosporine and tacrolimus, and cytotoxic drugs, such as cyclophosphamide, are also options in patients who fail standard therapy, including biologic agents.
-Consider IVIG

Fig. 6 NICE[203] UK Guidelines for treatment of JIA (2015)



B. Oligoarticular JIA

Fig. 1 ACR[35] Therapeutic approach (2021)



DMARD = disease-modifying antirheumatic drug, HCQ = hydroxychloroquine, JIA = juvenile idiopathic arthritis, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal antiinflammatory drugs, SSZ = sulfasalazine, TMJ = temporomandibular joint

Fig. 2 Indian Academy of Paediatrics[207] (2022)

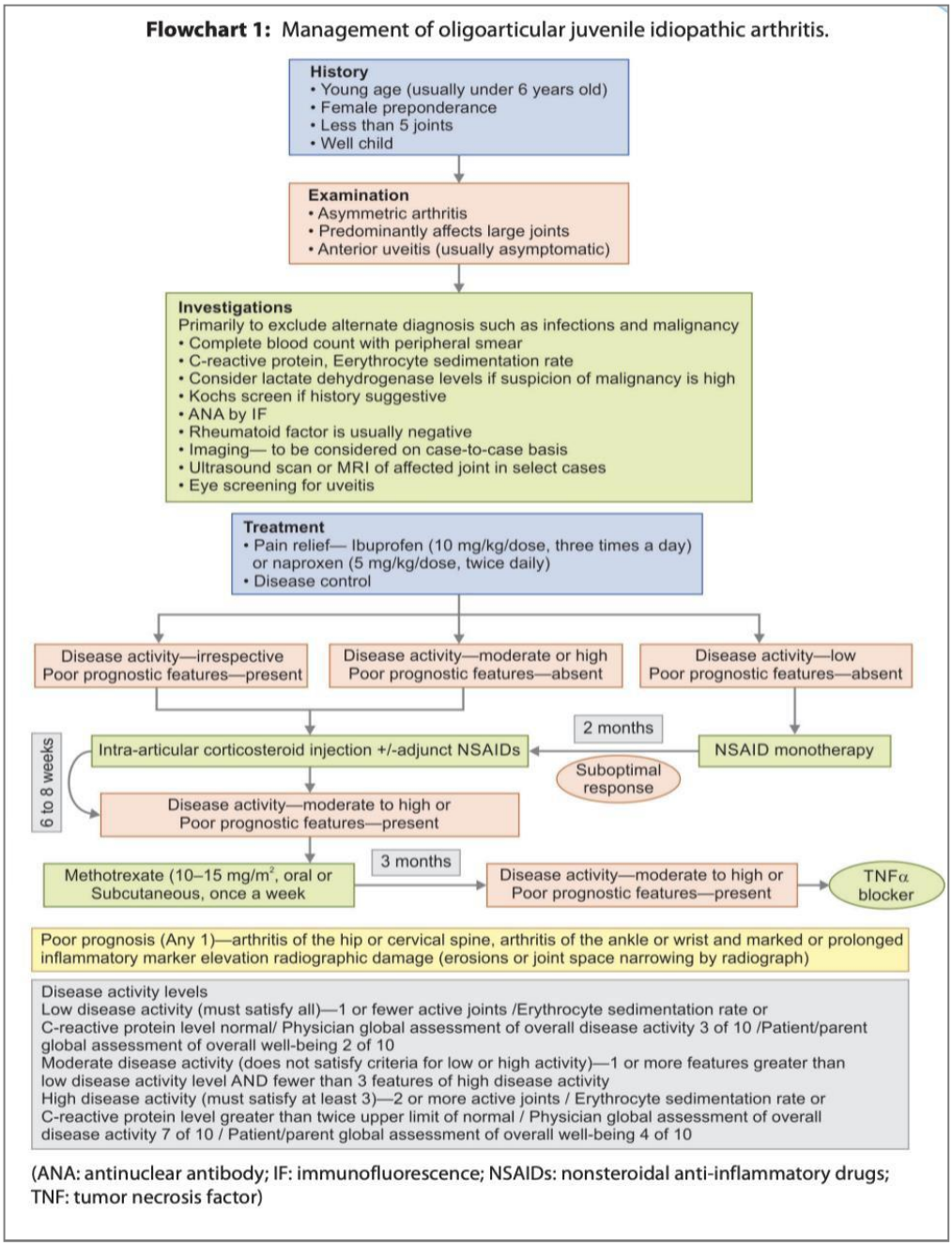
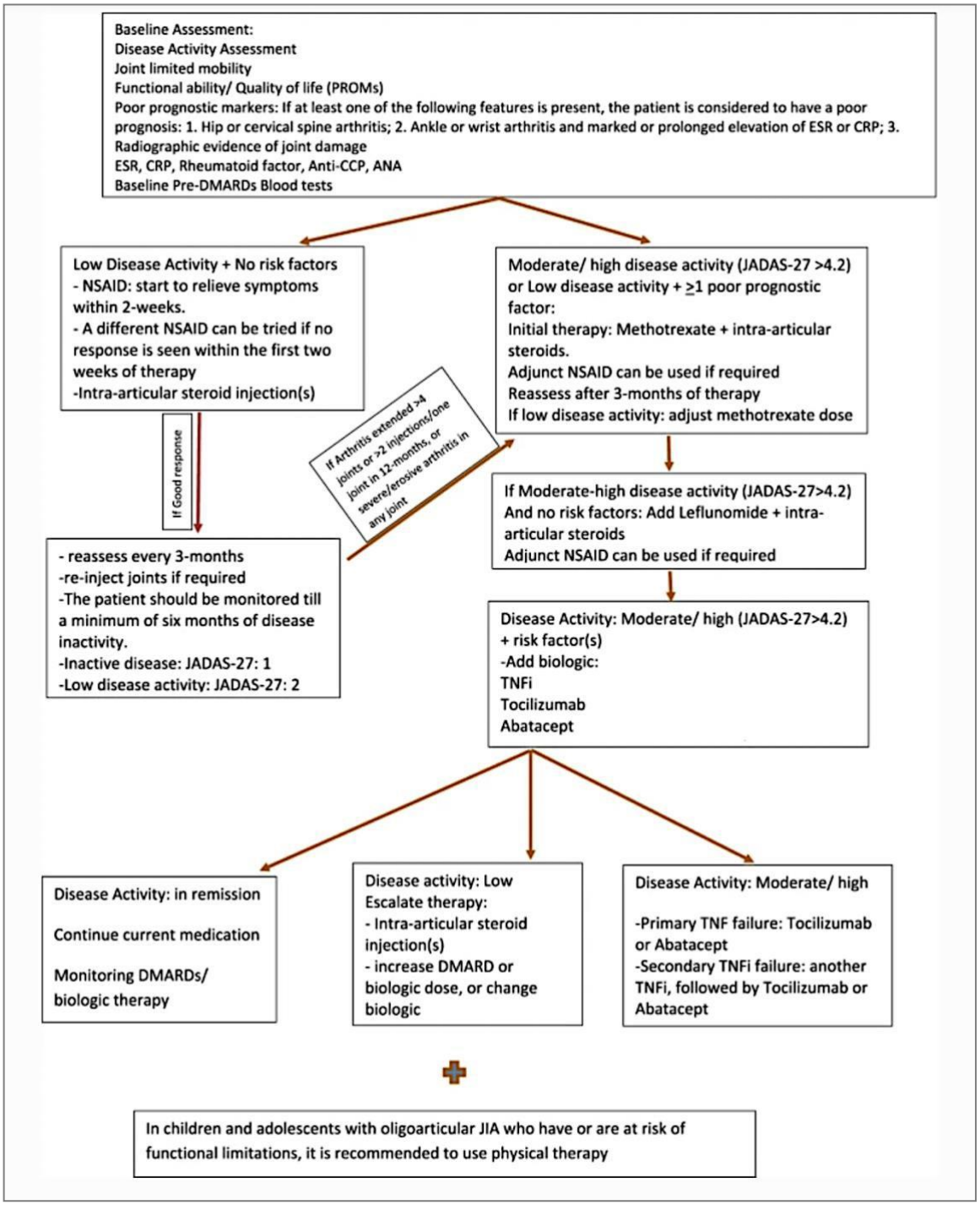


Fig. 3 Egyptian College of Paediatric Rheumatology[202] treat-to-target (2022) guidelines



C. Polyarticular JIA

Fig. 1 ACR[39] guideline (2019)

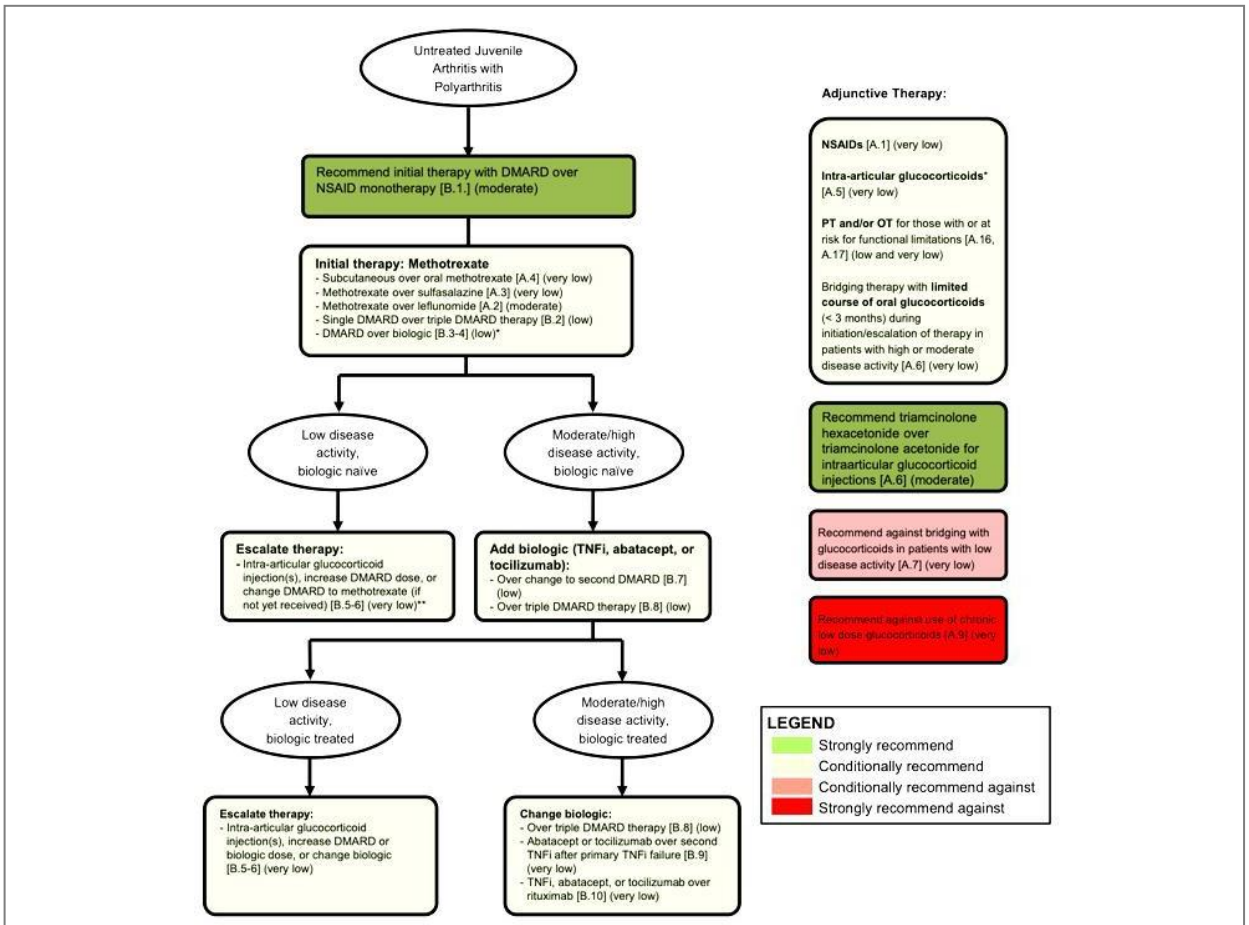
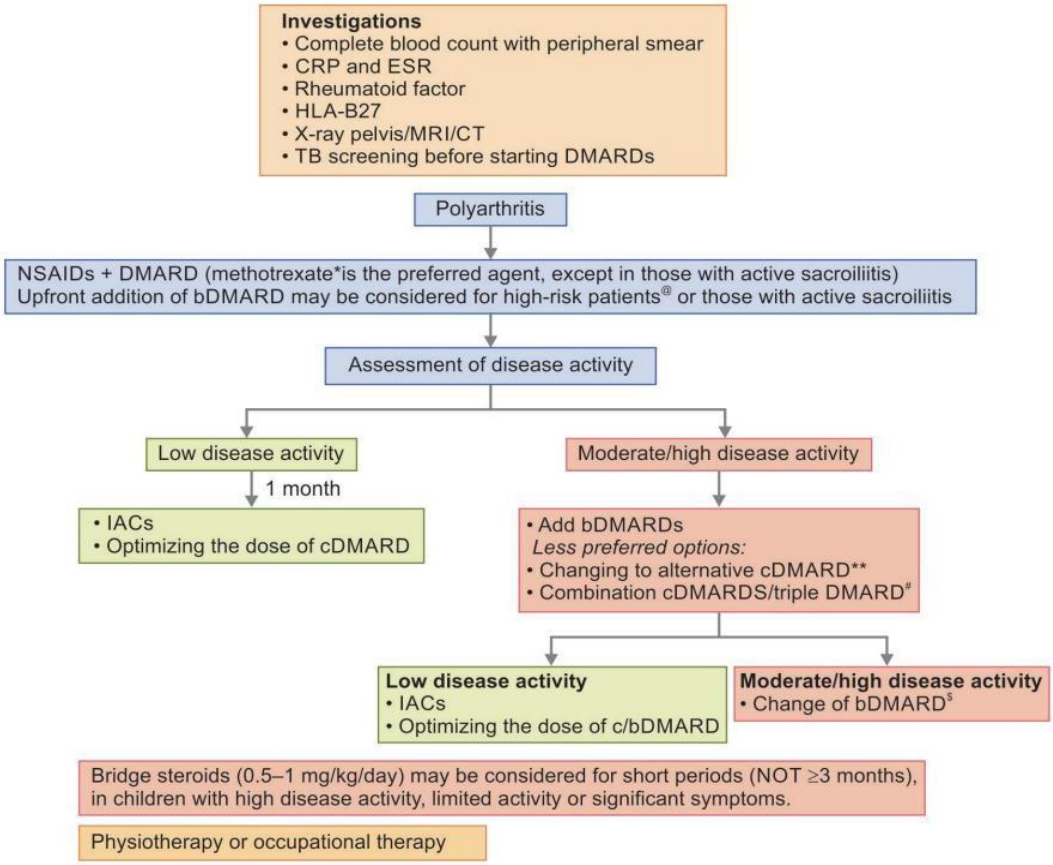


Figure 1. Summary of primary recommendations for the initial and subsequent treatment of children with juvenile idiopathic arthritis (JIA) and active polyarthritis (see also Tables 3 and 4; for patients with sacroiliitis and/or enthesitis, see also Tables 5 and 6). The clinical Juvenile Arthritis Disease Activity Score based on 10 joints (cJADAS-10) was used to define low disease activity (≤2.5 with ≥1 active joint) versus moderate/high disease activity (>2.5). Although it is provided as a general parameter, the cJADAS-10 should be interpreted within the clinical context. An adequate trial of methotrexate was considered to be 3 months. If no or minimal response is observed after 6–8 weeks, it was agreed that changing or adding therapy may be appropriate. Shared decision-making between the physician, parents, and patient, including discussion of recommended treatments and potential alternatives, is recommended when initiating or escalating treatment. The Patient/Population, Intervention, Comparison, and Outcomes (PICO) questions are shown in brackets, and quality of evidence is shown in parentheses. DMARD = disease-modifying antirheumatic drug; NSAID = nonsteroidal antiinflammatory drug; PT = physical therapy; OT = occupational therapy; TNFi = tumor necrosis factor inhibitor. *DMARD therapy (methotrexate, leflunomide, or sulfasalazine) over biologic recommendation for patients without and those with risk factors, although initial biologic therapy may be appropriate for some patients with risk factors and involvement of high-risk joints, high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage. **Adding a biologic may be considered in biologic-naive patients with continued low disease activity after escalating therapy (not formally addressed in the guidelines).

Fig. 2 Indian Academy of Paediatrics[207] (2022)

Flowchart 2: Management of polyarticular course of juvenile idiopathic arthritis (JIA).



Choice of bDMARD in order of preference: TNFi >> abatacept or tocilizumab > rituximab (only in RF positive polyarticular JIA)

@ Involvement of high-risk joints cervical spine, wrist or hip or those with high disease activity

* Sulfasalazine may be preferred in those with active sacroiliitis
Methotrexate: Subcutaneous route is preferred particularly at higher doses (>12.5 mg)

** Changing to another DMARD or combination DMARD seems a pragmatic approach in resource poor setting

Triple DMARDs: Methotrexate, hydroxychloroquine, and sulfasalazine

$ Switching to a non-TNFi (abatacept/tocilizumab) agent is preferred over switching to second anti-TNF. An alternative second anti-TNF agent may be appropriate for patients with good initial response to first anti-TNF.

(bDMARD: biological disease modifying anti-rheumatic drug; cDMARD: conventional disease modifying anti-rheumatic drug; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IACs: intra-articular corticosteroids, triamcinolone acetonide is used in India due to nonavailability of triamcinolone hexacetonide; NSAIDs: nonsteroidal anti-inflammatory drugs, naprosyn is the preferred agent; TB: tuberculosis; TNF: tumor necrosis factor)

Fig. 3 Egyptian College of Paediatric Rheumatology[202] treat-to-target guidelines (2022)

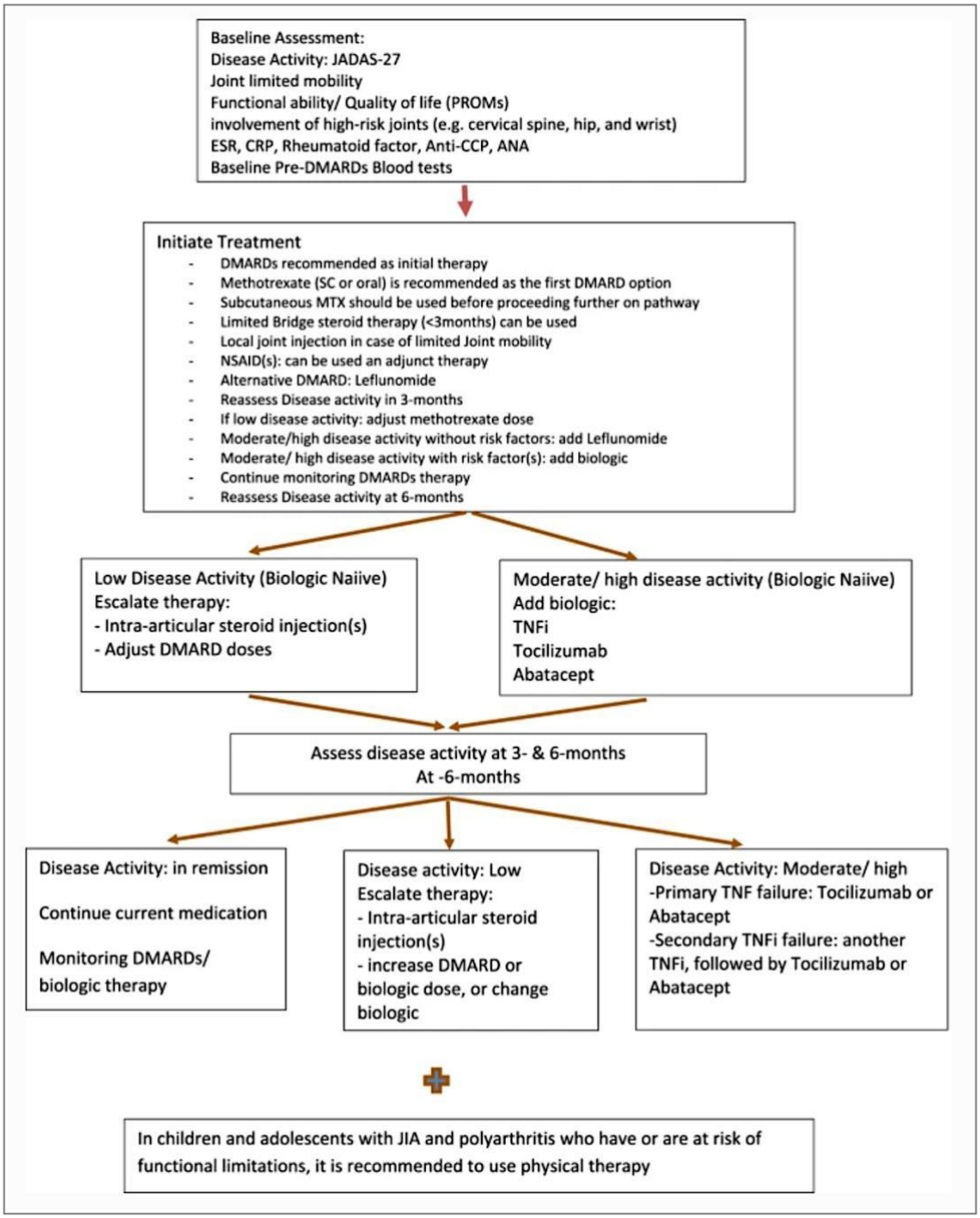
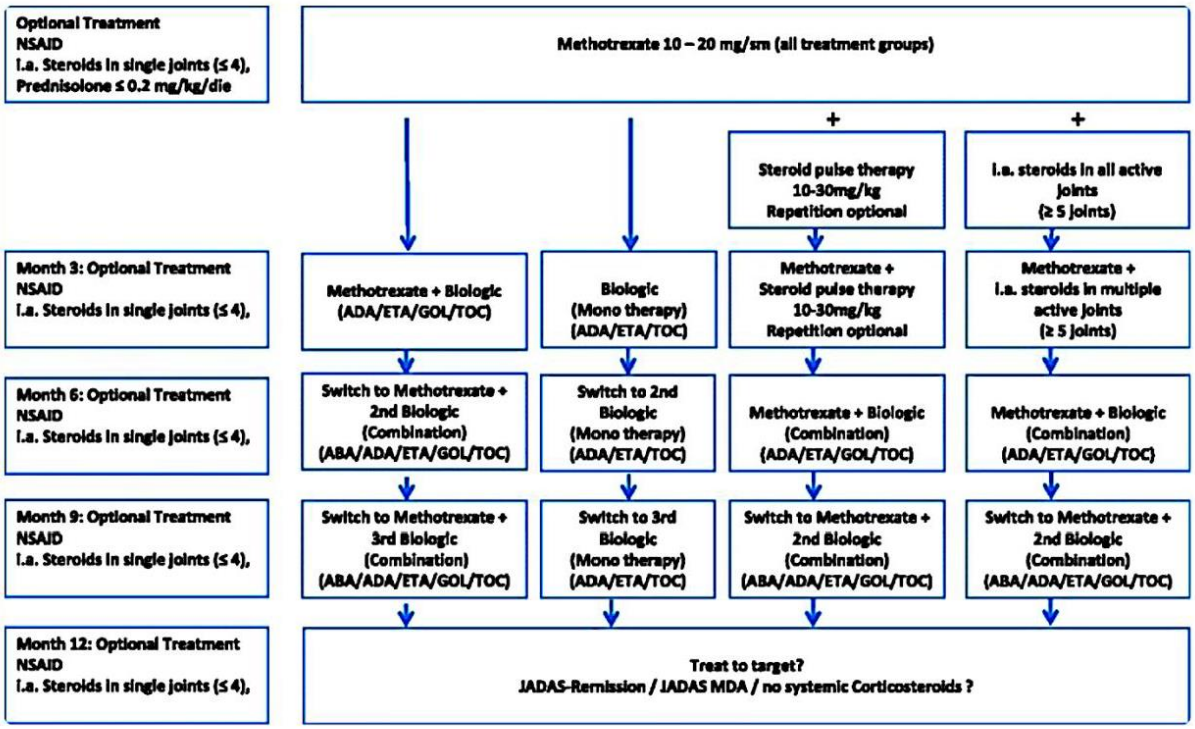
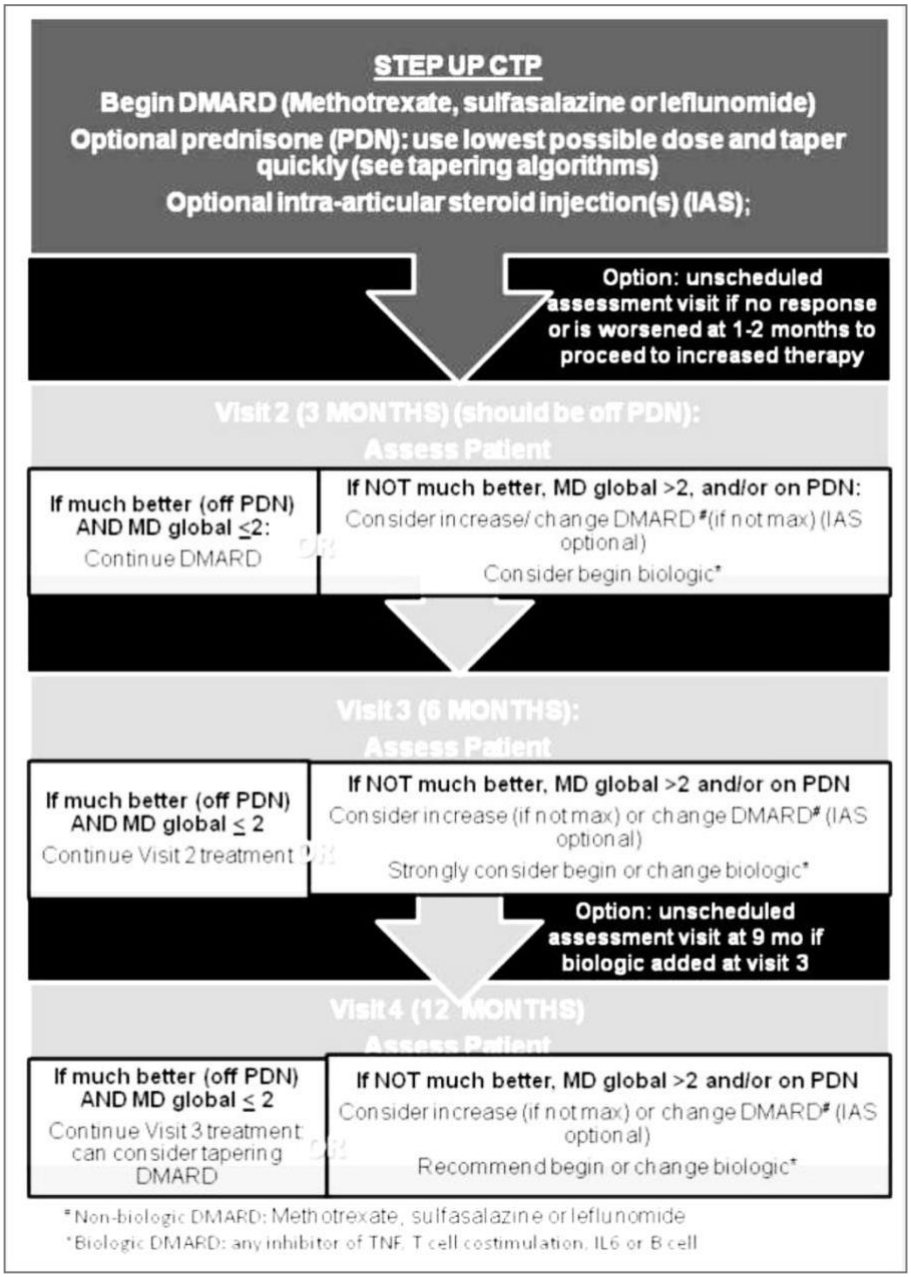


Fig. 4 German PRO-KIND[108] Treat-to-target guidelines (2017)



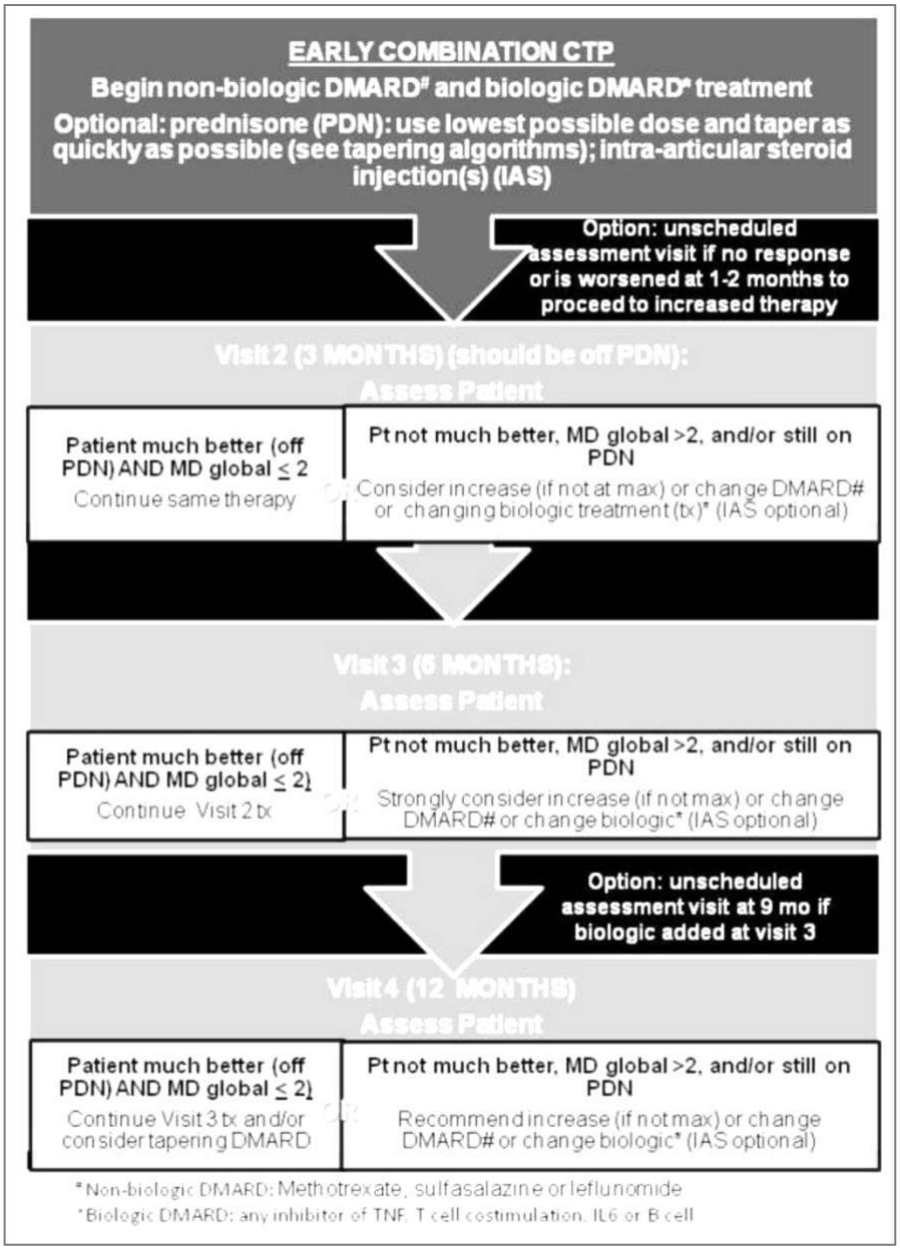
Therapeutic algorithm with 4 equally applicable consensus treatment plans. Initial treatment with methotrexate is intended for all patients with the diagnosis of polyarticular JIA. Non-steroidal-antiinflammatory drugs (NSAID) and up to 4 intraarticular joint injections with Triamcinolone hexacetonid are facultative on the discretion of the physician. Efficacy and tolerability should be evaluated every 3 months. The existing therapy will be continued if the therapeutic goals have been achieved, but should be altered if these have not been achieved. The treatment goals formulated for month 3, 6, 9 and 12 become more stringent with duration of therapy. The selection of the biologics is the responsibility of the treating physician. The approval for age and weight should be considered. ABA = abatacept, ADA = adalimumab, ETA = etanercept, GOL = golimumab, TOC = tocilizumab

Fig. 5(a) CARRA[204] Consensus Treatment Plans (2014): Step-up strategy



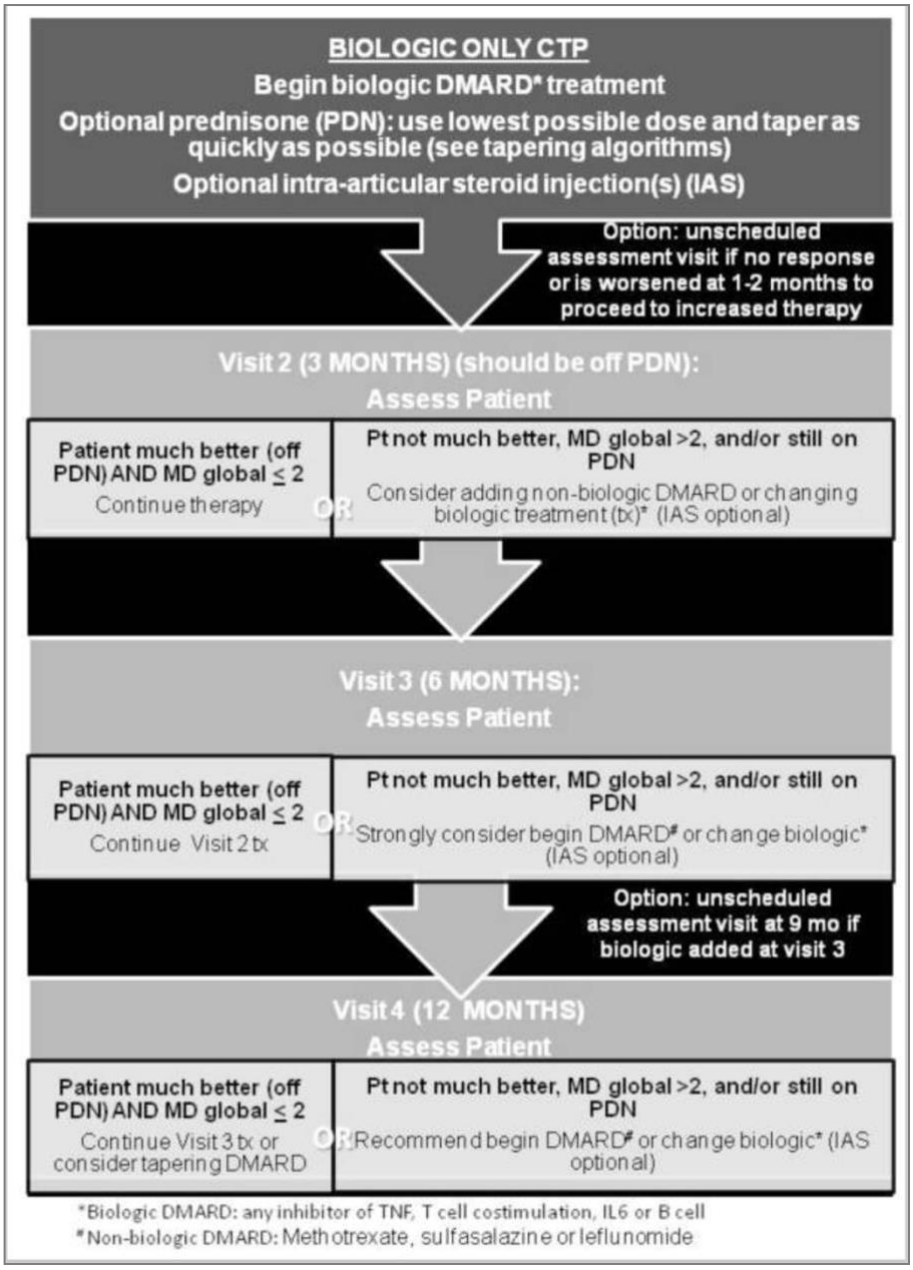
Non-biologic DMARD at treatment initiation followed by the option to start a biologic DMARD at 3 months or thereafter based on clinical assessment. DMARD choices include methotrexate, leflunomide, and sulfasalazine. Biologic choices include any inhibitor of TNF, T cell co-stimulation, IL6 or B cells.

Fig. 5(b) CARRA[204] Consensus Treatment Plans (2014): Early combination strategy



Early Combination Plan defined as a non-biologic and biologic DMARD combined within a month of treatment initiation. Biologic choices include any inhibitor of TNF, T cell co-stimulation, IL6 or B cells.

Fig. 5(c) CARRA[204] Consensus Treatment Plans (2014): Biologic only

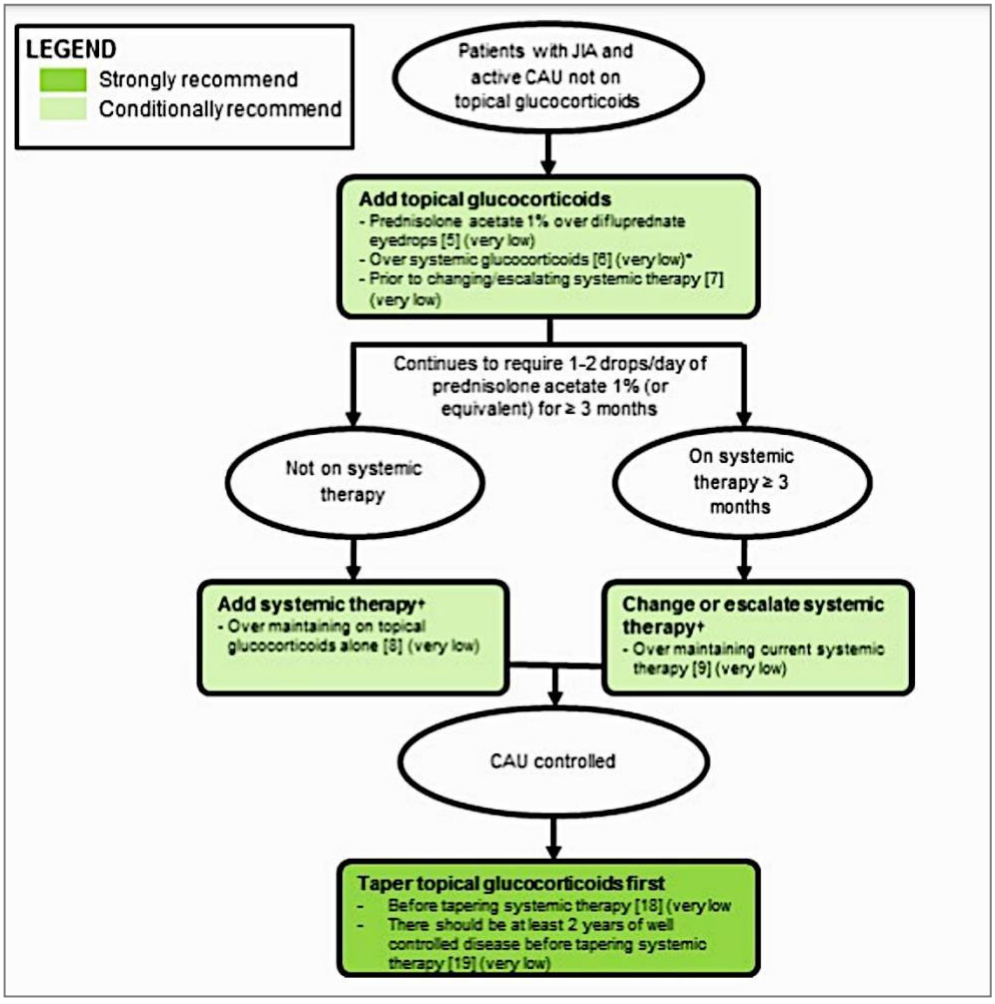


Biologic DMARD at treatment initiation followed by the option to start a non-biologic DMARD at 3 months or thereafter based on clinical assessment. DMARD= non-biologic DMARD; biologic= biologic DMARD; IAS= intraarticular glucocorticoid injection. DMARD choices include methotrexate, leflunomide, and sulfasalazine. Biologic choices include any inhibitor of TNF, T cell co-stimulation, IL6 or B cells.

D. JIA-associated Uveitis

Fig. 1 ACR[16] guideline (2019)

Recommendations for topical glucocorticoids in patients with juvenile idiopathic arthritis (JIA) and chronic anterior uveitis (CAU).



Systemic therapy is defined as disease-modifying antirheumatic drugs and biologics. Topical glucocorticoids refer to prednisolone acetate 1% (or equivalent). Doses of prednisolone acetate 1% greater than 1–2 drops/eye/day may be needed initially but increase the risk of ocular complications. Topical glucocorticoids should be used as short-term therapy (≤3 months). The goal is to discontinue topical glucocorticoid use, due to risk of glaucoma and cataracts. Periocular and intraocular injections are administered at the discretion of the treating ophthalmologist. The recommendation numbers are shown in brackets, and quality of evidence is shown in parentheses. * = In selected patients, systemic glucocorticoids can be used as short-term bridging therapy. † = Can escalate dose or frequency of current therapy; 3 months is the threshold for adding or changing systemic therapy in children who require topical glucocorticoids to maintain uveitis control. Changes in systemic therapy may be warranted earlier, depending on findings on the ocular examination, the duration of topical and systemic therapy, and the presence of existing complications

Fig. 2 German[205] Interdisciplinary guidelines (2019)

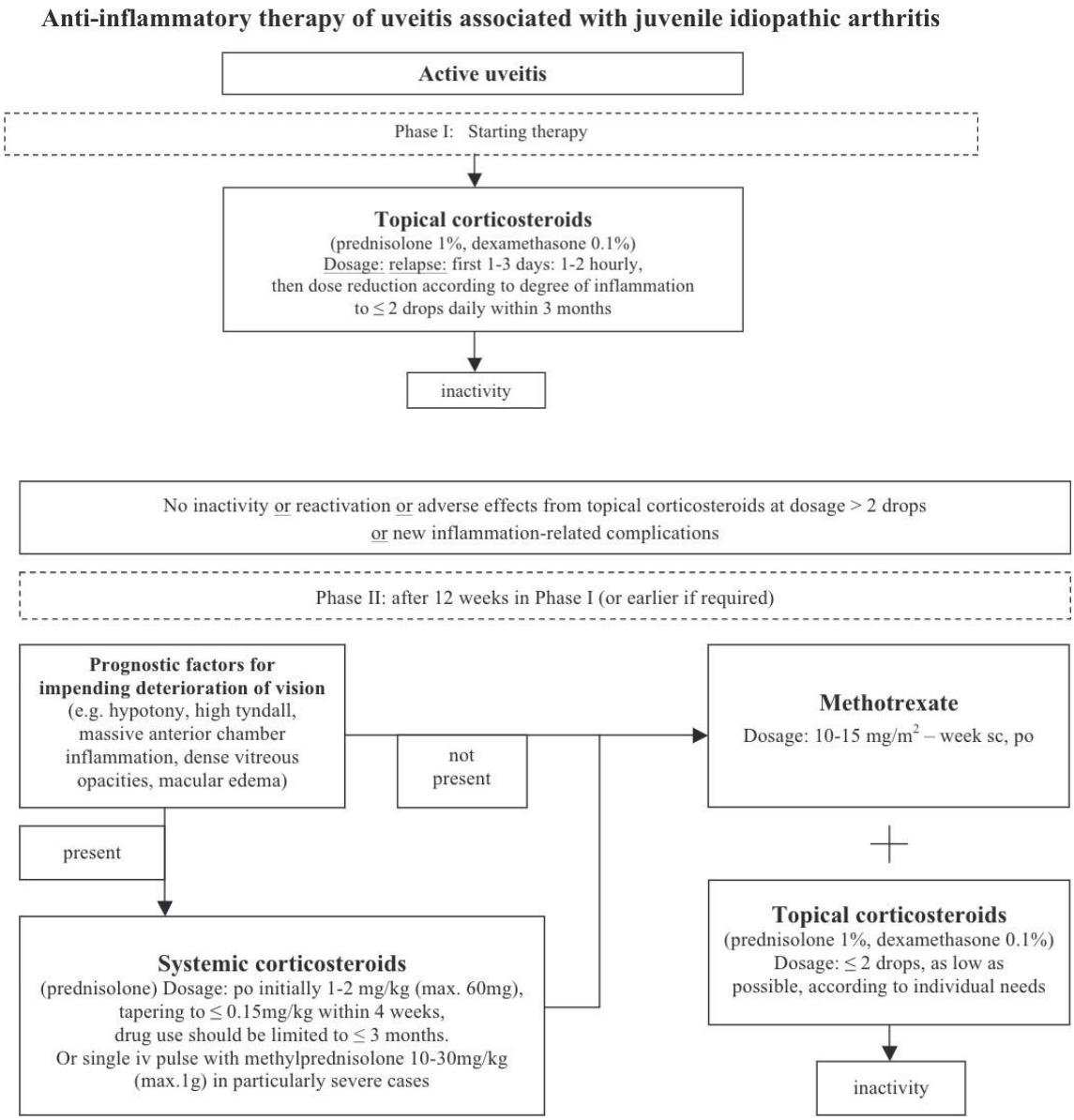


Fig. 2 German[205] Interdisciplinary guidelines (2019) continued

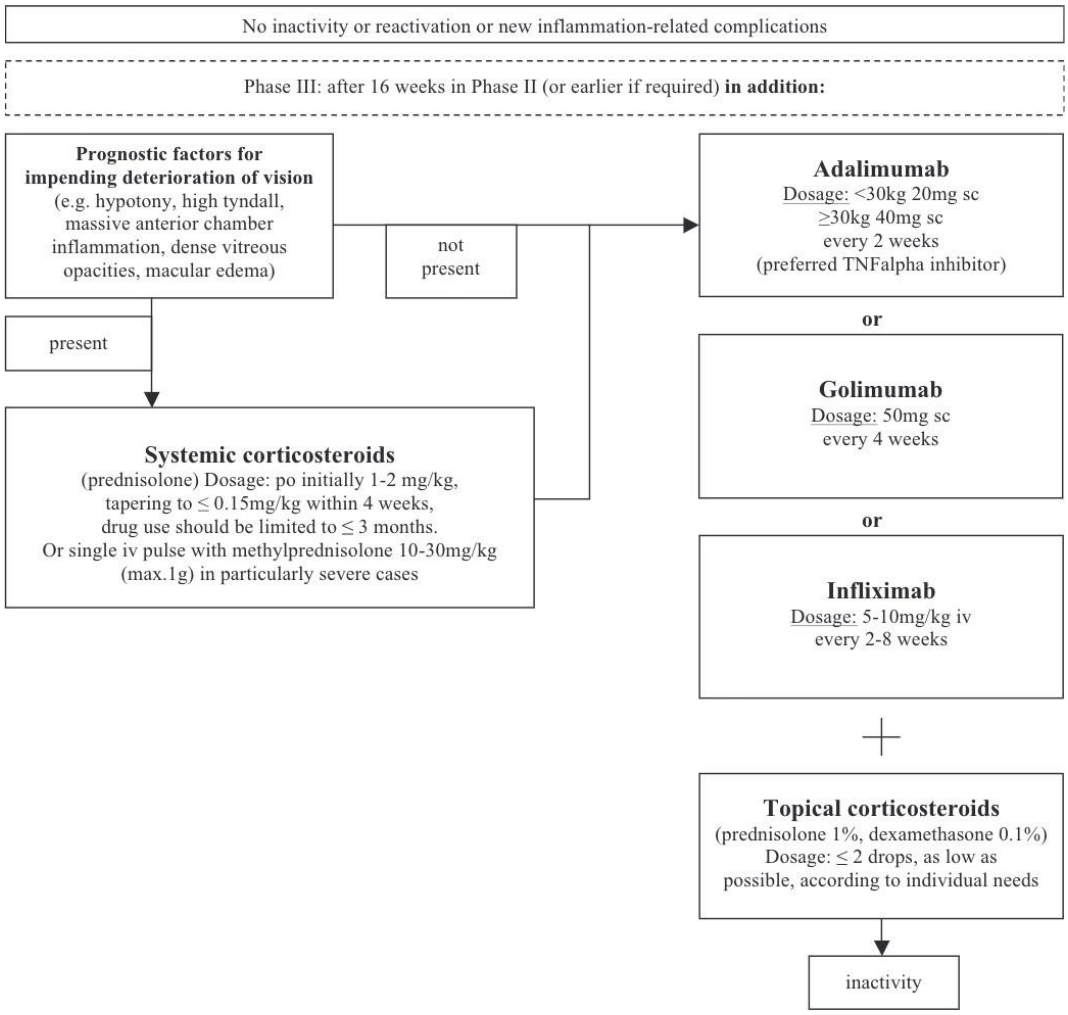
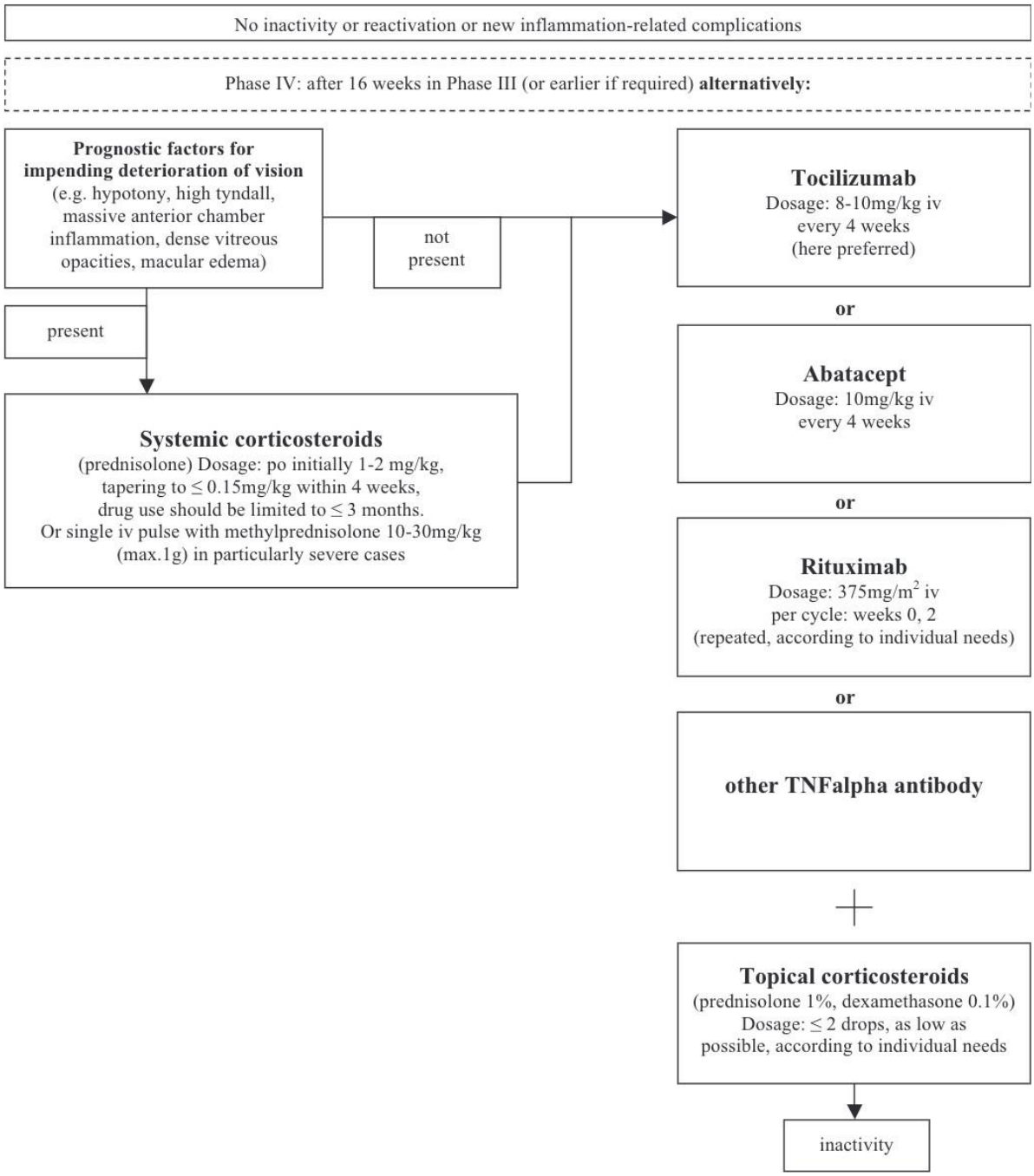


Fig. 2 German[205] Interdisciplinary guidelines (2019) continued



Phase I - IV: Anti-inflammatory therapy of uveitis associated with juvenile idiopathic arthritis
The dosages are intended to provide orientation and should always be adapted to the circumstances of the individual patient

Fig. 3 Egyptian College of Paediatric Rheumatology[202] (2022)

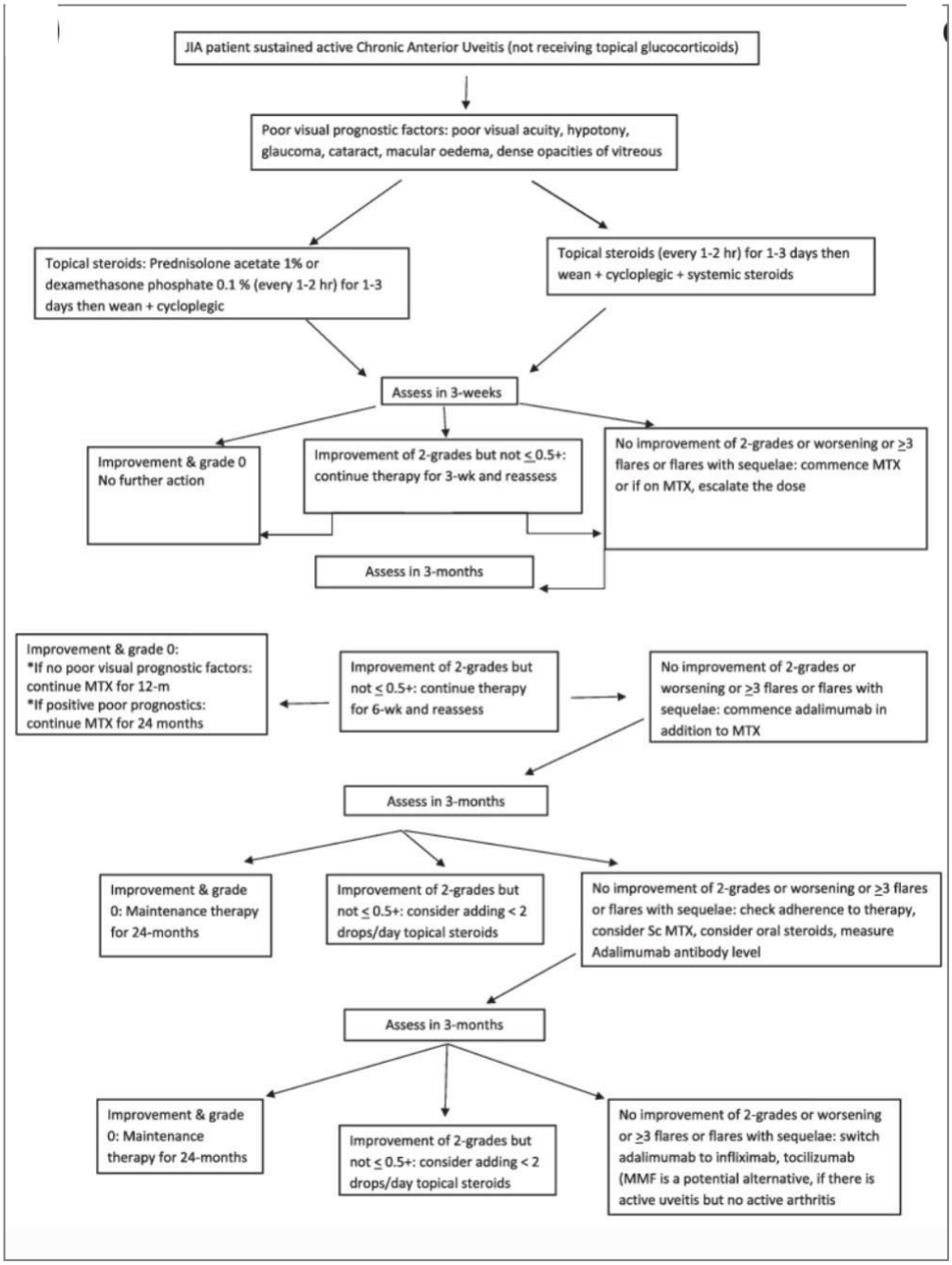


Fig. 4(a) CARRA[206] Consensus Treatment Plans (2019): Methotrexate

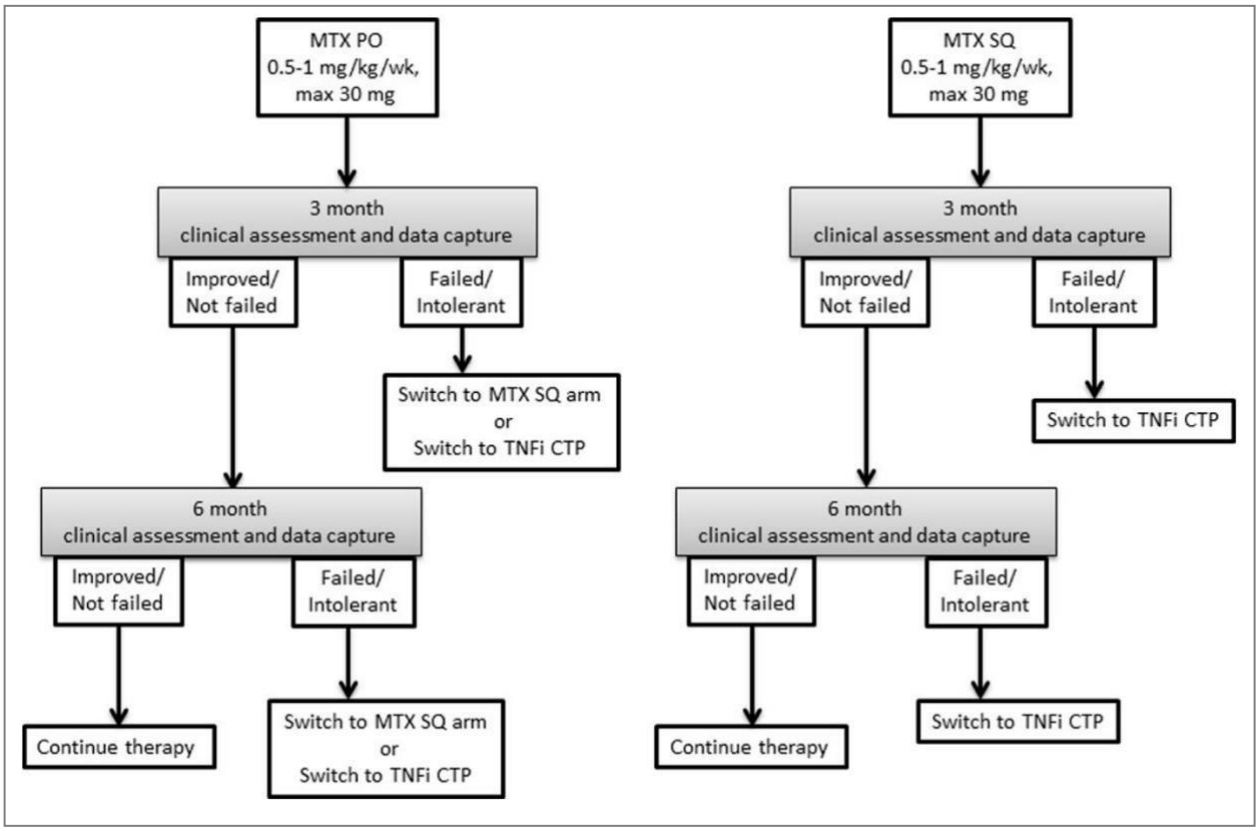
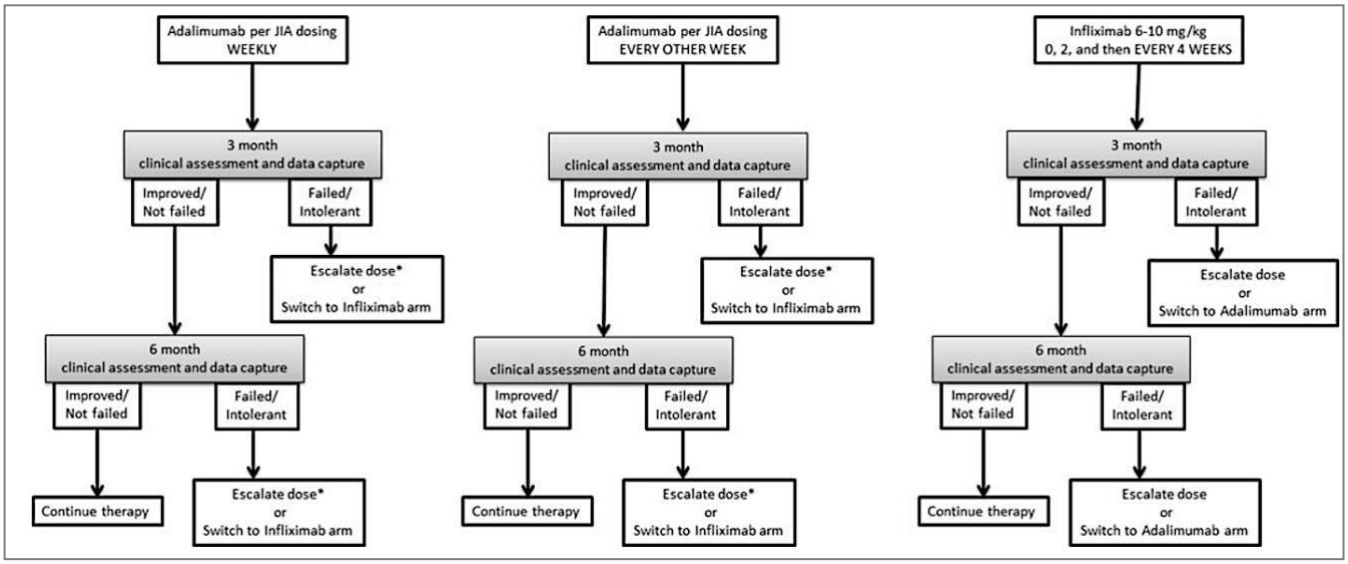


Fig. 4(b) CARRA[206] Consensus Treatment Plans (2019): TNFi



At all stages aim to minimise topical steroid to ≤ 2 drops/day while maintaining AC cell grade ≤ 0.5+. Mycophenolate mofetil (MMF) is a potential alternative to a biologic drug if there is active uveitis but no active arthritis.

AC: anterior chamber, d: days, h: hours, m: months, MTX: methotrexate, po: by mouth, sc: subcutaneous, tx: treatment, VA: visual acuity, w: weeks

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Contributions
The concept and case of need was led by HF, WS and CS. WS formulated the report supervised by CS and HF. All authors read and approved the final manuscript.

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