JUVENILE IDIOPATHIC ARTHRITIS (JIA)

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

INDICATION UPDATE

ADDENDUM- September 2023

To the CHI Original Juvenile idiopathic arthritis Clinical Guidance- Issued April 2020

Table of Contents

List of Tables

List of Figures

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

AAU	Acute Anterior Uveitis
ACT	Appropriate Comparator Therapy
ANA	Anti-Nuclear Antibody
CADTH	Canadian Agency for Drugs and Technologies in Health
CAU	Chronic Anterior Uveitis
CHI	Council of Health Insurance
CPG	Clinical Practice Guidelines
CTP	Consensus Treatment Plan
DMARD	Disease-Modifying Antirheumatic Drug
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAS	Haute Autorite de Sante
HCQ	Hydroxychloroquine
HTA	Health Technology Assessment
IAGCs	Intraarticular Glucocorticoids
IDF	CHI Drug Formulary
IL-1	Interleukin-1
IL-6	Interleukin-6
IQWIG	Institute for Quality and Efficiency in Health Care
JIA	Juvenile Idiopathic Arthritis
JIA-U	Juvenile Idiopathic Arthritis Associated Uveitis
LEF	Leflunomide
MAS	Macrophage Activation Syndrome
MTX	Methotrexate
NICE	National Institute for Health and Care Excellence
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PBAC	Pharmaceutical Benefits Advisory Committee
RF	Rheumatoid Factor
SFDA	Saudi Food and Drug Authority
SSZ	Sulfasalazine
TMJ	Temporomandibular Joint
TNFi	Tumor Necrosis Factor inhibitor

Executive Summary

Juvenile idiopathic arthritis (JIA), previously termed juvenile rheumatoid arthritis, is the prevalent form of arthritis in individuals under 16 years old.

Symptom duration varies among children, with some experiencing them for a short period while others endure them for many years. Without effective management, these symptoms can lead to persistent joint pain, stiffness, swelling, and potentially leading to joint damage[1].

Worldwide, around 3 million children and adolescents are afflicted by JIA, and the occurrence is consistently more common in females. The Africa and Middle East region is marked by a varied mix of ethnicities, economic circumstances, and climates, all of which contribute to the prevalence of JIA. There is a limited number of studies that have been published on the epidemiology of JIA in this region[2].

A study was conducted in a Pediatric Rheumatology clinic in a single tertiary center Saudi Arabia to evaluate the Pattern of JIA. Medical records of all patients who are followed up between January 2007 and January 2015 were retrospectively reviewed. The overall number of patients amounted to 82, with males accounting for 31 individuals (37.8%). The average age at which JIA began was 7.1 years, with a standard deviation of 3.6 years. The average duration of follow-up was approximately 2.67 years, with a standard deviation of 1.6 years. Systemic JIA was the most prevalent subtype, constituting 36.5% of cases, followed by polyarticular at 29.2% and oligoarticular at 28%[3].

Some forms of JIA may lead to notable complications such as stunted growth, joint damage, and uveitis. The primary focus of treatment revolves around managing pain and inflammation, improving overall functionality, and preventing further damage[1].

CHI issued JIA clinical guidance after thorough review of renowned international and national clinical guidelines in April 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI JIA clinical guidance and seeks to offer guidance for the effective management of JIA. It provides an **update on the** JIA **Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the addition of new guidelines to the report such as 2021 American College of Rheumatology (ACR) Guideline** for the Treatment of JIA: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint (TMJ) Arthritis, and Systemic JIA, **2021 ACR Guideline** for the Treatment of JIA: Recommendations for Nonpharmacologic Therapies,

Medication Monitoring, Immunizations, and Imaging, **2019 ACR/Arthritis Foundation Guideline** for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis (JIA-U), **Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus** treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis **(2019)**, and **The 2021 Portuguese Society of Ophthalmology joint guidelines with Paediatric Rheumatology** on the screening, monitoring and medical treatment of JIA-U.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include a new dose of adalimumab (80 mg), oral solution form of methotrexate (2 mg/mL), prednisolone effervescent tablets (5 and 2 mg) as well as syrup (3 mg/mL) in the CHI formulary for JIA. Moreover, it is also recommended to add the SFDA registered drugs **Anakinra (KINERET®)**, **Tofacitinib (XELJANZ®)** and **Golimumab (SIMPONI®)** to the CHI formulary for juvenile idiopathic arthritis.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the JIA therapeutic management.

Below is a table summarizing the major changes based on the different JIA guidelines used to issue this report.

Table 1. General Recommendations for the Management of Juvenile idiopathic Arthritis

Management of JIA		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
The use of NSAIDs is conditionally recommended as first-line therapy for oligoarthritis, TMJ arthritis and systemic JIA.	Certainty of evidence: very low	2021 American College of Rheumatology (ACR) Guideline[4]
Intraarticular glucocorticoids (IAGCs) are strongly recommended as initial therapy for the management of oligoarthritis. Triamcinolone hexacetonide is strongly recommended as the preferred agent.	Certainty of evidence: very low	2021 ACR Guideline[4]
Conventional synthetic DMARDs are strongly advised for cases of insufficient response to/or intolerance of NSAIDs	Not graded	2021 ACR Guideline[4]

and/or IAGCs when managing cases of oligoarthritis and TMJ arthritis.		
Methotrexate is conditionally recommended as a preferred agent over LEF, SSZ, and HCQ (in that order) for the treatment of oligoarthritis.	Certainty of evidence: Low (MTX); Very low (LEF, SSZ, HCQ)	2021 ACR Guideline[4]
In the management of TMJ arthritis, MTX is conditionally recommended as a preferable option over LEF.	Certainty of evidence: very low	2021 ACR Guideline[4]
Biologic DMARDs are strongly advised in cases of insufficient response to/or intolerance of NSAIDs and/or IAGCs, along with the use of at least one conventional synthetic DMARD in the treatment of oligoarthritis.	Certainty of evidence: very low	2021 ACR Guideline [4]
Biologic DMARDs, without preference for one agent over the other, are conditionally recommended in cases of insufficient response to/or intolerance of NSAIDs and/or IAGCs, along with the utilization of at least one conventional synthetic DMARD for the management of TMJ arthritis.	Certainty of evidence: very low	2021 ACR Guideline[4]
The suggested approach for treating active uveitis involves using potent topical steroids as the initial treatment. It is advised to start with a concentrated application, followed by a gradual tapering regimen.	Not graded	The 2021 Portuguese Society of Ophthalmology joint guidelines with Paediatric Rheumatology[5]
For children and adolescents diagnosed with JIA and severe active CAU accompanied by sight-threatening complications, it is conditionally recommended to initiate both methotrexate and a monoclonal antibody TNFi promptly, in preference to using methotrexate alone.	Not graded	2019 American College of Rheumatology/ Arthritis Foundation Guideline [6]
For children and adolescents diagnosed with JIA and active CAU who are initiating	Not graded	2019 ACR/

a TNFi treatment, the initiation of a monoclonal antibody TNFi over etanercept is conditionally recommended.		Arthritis Foundation Guideline[6]
In cases where children and adolescents with JIA and active CAU exhibit an inadequate response to a monoclonal antibody TNFi at the standard JIA dose, an increase in the dose and/or frequency above the standard level is conditionally recommended instead of switching to a different monoclonal antibody TNFi.	Not graded	2019 ACR/ Arthritis Foundation Guideline[6]
When children and adolescents with JIA and active CAU do not experience success with the first monoclonal antibody TNFi even when administered at an escalated dose and/or frequency, changing to another monoclonal antibody TNFi is conditionally recommended rather than transitioning to a biologic from another category.	Not graded	2019 ACR/ Arthritis Foundation Guideline
In situations where children and adolescents with JIA and active CAU do not achieve desired outcomes after trying methotrexate and two monoclonal antibody TNFi treatments at an above-standard dose and/or frequency, the use of abatacept or tocilizumab as biologic DMARD options, along with mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic DMARD options, is conditionally recommended	Not graded	2019 ACR/ Arthritis Foundation Guideline

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI JIA report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

There are no updated guidelines for this indication since April 2020.

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
American College of Rheumatology (ACR)/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non- Systemic Polyarthritis, Sacroiliitis, and Enthesitis (**2019**)	N/A*
NICE Guidelines for Abatacept, Adalimumab, Etanercept and Abatacept, Adalimumab, Etanercept and Tocilizumab for Treating Juvenile Idiopathic Arthritis (**2015**)	N/A*
Management of Juvenile Idiopathic Arthritis: A Position Statement from the **Pediatric Committee of the Canadian Rheumatology Association** (**2015**)	N/A*
2013 Update of the 2011 **American College of Rheumatology (ACR)** Recommendations for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for the Medical Therapy of Children with Systemic Juvenile Idiopathic Arthritis and Tuberculosis Screening Among Children Receiving Biologic Medications	N/A*

**: No updated version available:* the existing version is the most recent one and no further updates or revisions have been made or released.

1.2. Additional Guidelines

This section includes the added guidelines to the previous CHI JIA report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
2021 American College of Rheumatology (ACR) Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis
2021 American College of Rheumatology (ACR) Guideline for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging
2019 American College of Rheumatology (ACR)/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis
Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis **(2019)**
The 2021 Portuguese Society of Ophthalmology joint guidelines with Paediatric Rheumatology on the screening, monitoring and medical treatment of juvenile idiopathic arthritis-associated uveitis

1.2.1 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis (2021)

The 2021 ACR Guideline for the Treatment of JIA: Therapeutic Approaches for Oligoarthritis, TMJ Arthritis, and Systemic JIA[4] introduced methods for grading, as explained below:

- "Quality assessment was performed separately for each outcome using the GRADE system, which results in one of four possible evidence grades that reflect level of confidence in the effect estimate: high, moderate, low, and very low."
- "In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low quality evidence almost invariably mandates a weak recommendation."

- "There are, however, situations in which low quality evidence can lead to strong recommendations. For instance, if there is low quality evidence favoring an intervention but high-quality evidence of important harm then a strong recommendation against the intervention may be appropriate."
- "According to GRADE, a recommendation is categorized as strong if the panel is very confident that the benefits of an intervention clearly outweigh the harms (or vice versa); a conditional recommendation denotes uncertainty regarding the balance of benefits and harms, such as when the evidence quality is low or very low, or when the decision is sensitive to individual patient preferences, or when costs are expected to impact the decision."

Oligoarticular JIA

Oligoarthritis refers to JIA presenting with involvement of ≤4 joints without systemic manifestations.

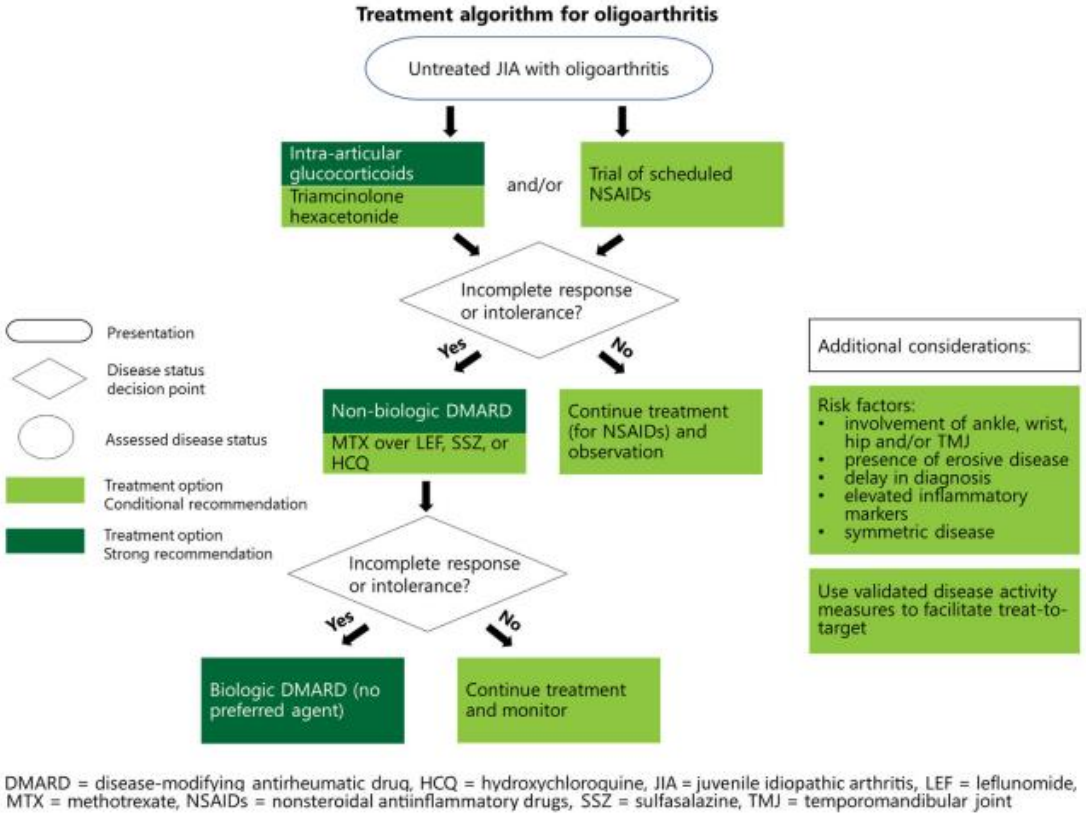
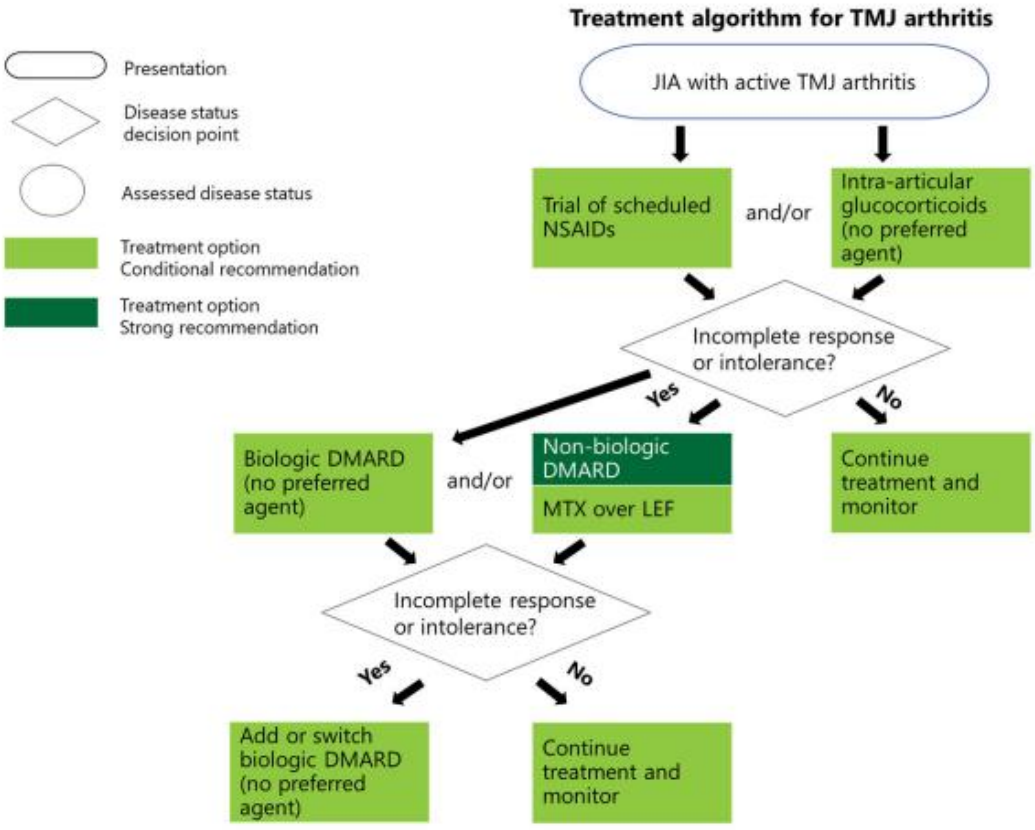


Figure 1. *Treatment Algorithm for Oligoarthritis. Retrieved from Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2022;74(4):521-537. doi:10.1002/acr.24853.*

- It is **conditionally** recommended to use scheduled NSAIDs as part of initial therapy (Certainty of evidence: very low).
- Intraarticular glucocorticoids (IAGCs) are **strongly** recommended as part of initial therapy (Certainty of evidence: very low).
- Triamcinolone hexacetonide is **strongly** recommended as the preferred agent (Certainty of evidence: low).
- Oral glucocorticoids are **conditionally** recommended against as part of initial therapy (Certainty of evidence: very low).
- Conventional synthetic Disease-Modifying Antirheumatic Drugs (DMARDs) are **strongly** recommended if there is an inadequate response to scheduled NSAIDs and/or IAGCs. Methotrexate (MTX) is **conditionally** recommended as a preferred agent over Leflunomide (LEF), Sulfasalazine (SSZ), and Hydroxychloroquine (HCQ) (Certainty of evidence: Low (MTX); Very low (LEF, SSZ, HCQ)
- Biologic DMARDs are **strongly** recommended if there is inadequate response to/or intolerance of NSAIDs and/or IAGCs and at least 1 conventional synthetic DMARD. There is no preferred biologic DMARD (Certainty of evidence: very low).
- Considering risk factors for a poor outcome (such as the involvement of the ankle, wrist, hip, sacroiliac joint, and/or TMJ, the presence of erosive disease or enthesitis, a delay in diagnosis, elevated levels of inflammation markers, and symmetric disease) is **conditionally** recommended to guide decisions regarding treatment (Certainty of evidence: very low).
- The use of validated measures for assessing disease activity is **conditionally** recommended to aid in making treatment decisions, particularly to support the implementation of treat-to-target strategies (Certainty of evidence: very low).

Temporomandibular joint arthritis (TMJ)

- TMJ arthritis could exist independently or be a component of widespread arthritis. Managing TMJ arthritis is crucial, given that patients and caregivers have highlighted its significant effects on the quality of oral health-related life and difficulties in diagnosing and achieving effective pharmacological remedies.



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

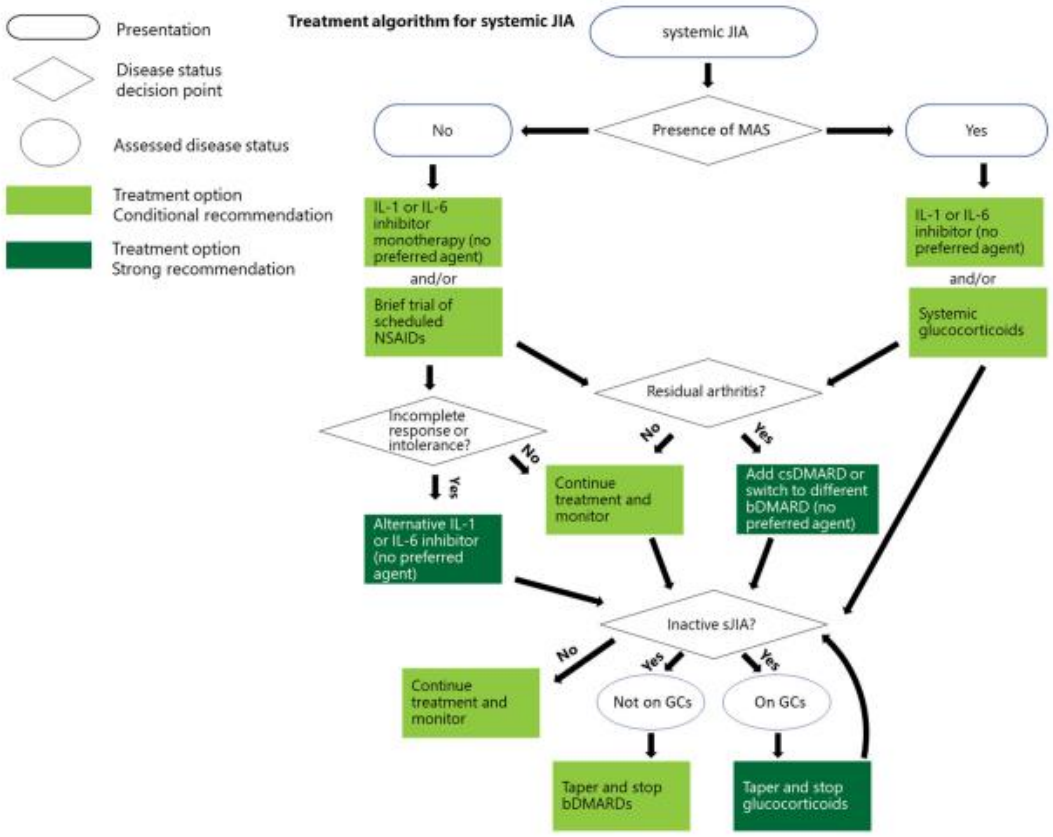
Figure 2. *Treatment Algorithm for Temporomandibular Joint Arthritis. Retrieved from Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2022;74(4):521-537. doi:10.1002/acr.24853*

- A trial of scheduled NSAIDs is **conditionally** recommended as part of initial therapy (Certainty of evidence: very low).
- IAGCs are **conditionally** recommended as part of initial therapy (Certainty of evidence: very low). There is no preferred agent (Certainty of evidence: very low).
- Oral glucocorticoids are **conditionally** recommended against as part of initial therapy (Certainty of evidence: very low).
- Conventional synthetic DMARDs are strongly **recommended** for inadequate response to or intolerance of NSAIDs and/or IAGCs. MTX is conditionally recommended as a preferred agent over LEF (Certainty of evidence: very low).

- Biologic DMARDs are **conditionally** recommended for inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 conventional synthetic DMARD. There is no preferred biologic agent (Certainty of evidence: very low).
- The evaluation of unfavorable predictive characteristics (such as the engagement of the ankle, wrist, hip, sacroiliac joint, and/or TMJ, existence of erosive disease or enthesitis, delayed diagnosis, elevated inflammation marker levels, and symmetrical disease) is **conditionally** recommended for informing decisions related to treatment (Certainty of evidence: very low).

Systemic JIA

- Systemic JIA stands apart from other forms of JIA due to the presence of fever, rash, and internal organ participation. Some experts view it as an autoinflammatory disorder.



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

Figure 3. *Treatment Algorithm for Systemic Juvenile Idiopathic Arthritis With or Without Macrophage Activation Syndrome. Retrieved from Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2022;74(4):521-537. doi:10.1002/acr.24853.*

Systemic JIA without macrophage activation syndrome (MAS)

- NSAIDs are **conditionally** recommended as initial monotherapy.
- Oral glucocorticoids are **conditionally** recommended against as initial monotherapy (Certainty of evidence: very low).
- Conventional synthetic DMARDs are **strongly** recommended against as initial monotherapy (Certainty of evidence: very low).
- Biologic DMARDs (Interleukin-1 (IL-1) and Interleukin-6 (IL-6) inhibitors) are **conditionally** recommended as initial monotherapy. There is no preferred agent (Certainty of evidence: very low).
- IL-1 and IL-6 inhibitors are **strongly** recommended over a single or combination of conventional synthetic DMARDs for inadequate response to or intolerance of NSAIDs and/or glucocorticoids (Certainty of evidence: very low).
- Biologic DMARDs or conventional synthetic DMARDs are **strongly** recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/ or IL-6 inhibitors. There is no preferred agent (Certainty of evidence: very low).

Systemic JIA with MAS

- IL-1 and IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS. Glucocorticoids are **conditionally** recommended as part of initial treatment of systemic JIA with MAS. There is no preferred agent (Certainty of evidence: very low).
- Biologic DMARDs or conventional synthetic DMARDs are **strongly** recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors. There is no preferred agent (Certainty of evidence: very low).

Systemic JIA with inactive disease

- Tapering down and discontinuing the use of glucocorticoids is **strongly** advised once a state of inactive disease has been achieved (Certainty of evidence: very low).
- Tapering and discontinuing biologic DMARDs is **conditionally** recommended after inactive disease has been reached (Certainty of evidence: very low).

1.2.2 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging (2021)

The 2021 ACR Guideline for the Treatment of JIA: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging[7] utilized the same grading scheme detailed in section 1.2.1 above.

Nonpharmacologic therapies

- A discussion of a healthy, age-appropriate diet is strongly recommended (Certainty of evidence: very low).
- Use of a specific diet to treat JIA is strongly recommended against (Certainty of evidence: very low).
- Use of supplemental or herbal interventions specifically to treat JIA is conditionally recommended against (Certainty of evidence: very low).
- Physical and occupational therapy are conditionally recommended regardless of concomitant pharmacologic therapy (Certainty of evidence: very low).

Medication monitoring

- NSAIDs: Monitoring via CBC counts, liver function tests (LFTs), and renal function tests every 6–12 months is **conditionally** recommended (Certainty of evidence: very low).
- MTX: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **strongly** recommended (Certainty of evidence: very low).
- Decreasing the MTX dosage or withholding MTX is **conditionally** recommended in the presence of a clinically significant increase in LFTs readings or a decrease in neutrophil or platelet counts (Certainty of evidence: very low).
- Use of folic/folinic acid in conjunction with MTX is **strongly** recommended (Certainty of evidence: very low).
- SSZ: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended (Certainty of evidence: very low).
- Decreasing the SSZ dosage or withholding SSZ is **conditionally** recommended if a clinically relevant elevation in LFTs or decreased neutrophil or platelet count is detected (Certainty of evidence: very low)

- LEF: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3-4 months thereafter is **conditionally** recommended (Certainty of evidence: very low)
- Altering LEF administration is **conditionally** recommended if a clinically relevant elevation in LFT results occurs (temporary withholding of LEF if the ALT level is >3 times the upper limit of normal [ULN]), as per the package insert (Certainty of evidence: very low).
- Baseline and annual retinal screening after starting HCQ are **conditionally** recommended (Certainty of evidence: very low).
- HCQ: Monitoring via CBC counts and LFTs annually is **conditionally** recommended (Certainty of evidence: very low).
- TNFi: Monitoring via CBC counts and LFTs annually is **conditionally** recommended (Certainty of evidence: very low).
- Abatacept: Doing no routine laboratory monitoring is **conditionally** recommended (Certainty of evidence: very low).
- Tocilizumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels every 6 months is conditionally recommended, as per the package insert (Certainty of evidence: very low).
- Anakinra: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended (Certainty of evidence: very low).
- Canakinumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended (Certainty of evidence: very low).
- Tofacitinib: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels 1–2 months after starting treatment is **conditionally** recommended, as per the package insert. Altering tofacitinib administration is strongly recommended if monitoring reveals laboratory abnormalities of concern. Specifically, medication should be discontinued if the hemoglobin level is 2 gm/dl, or for severe neutropenia (<500/mm3) or lymphopenia (<500/ mm3), as per the package insert (Given recent approval for JIA and limited experience, recommendations are based on clinical trial, US Food and Drug Administration guidance, and evidence in adult)

Infection surveillance/immunizations

- No consensus was achieved regarding the need to obtain infection titers (measles, varicella, hepatitis B, hepatitis C) for all children with JIA checked prior to starting immunosuppressive medication. (Certainty of evidence: very low).
- Immunization is **conditionally** recommended for children with active non-systemic JIA who have not yet been immunized for measles, mumps, rubella, and/or varicella prior to starting immunosuppressive medications. (Certainty of evidence: very low).
- Tuberculosis (TB) screening is **conditionally** recommended prior to starting biologic DMARD therapy and when there is a concern for TB exposure thereafter. (Certainty of evidence: very low).
- Immunizations (live and inactivated) are **strongly** recommended for children with JIA who are not receiving immunosuppressive treatment. (Certainty of evidence: very low).
- Annual inactivated influenza immunization is **strongly** recommended for all children with JIA. (Certainty of evidence: very low).
- Inactivated vaccines are **strongly** recommended for children who are receiving immunosuppressive treatment (Certainty of evidence: very low).
- Live attenuated vaccines are **conditionally** recommended against in children with JIA who are receiving immunosuppressive treatment. (Certainty of evidence: low).
- Vaccines are **strongly** recommended for household contacts of children with JIA who are receiving immunosuppressive treatment. (Certainty of evidence: very low).

Imaging

- Use of radiography as a screening test prior to advanced imaging, for the purpose of identifying active synovitis or enthesitis, is **strongly** recommended against. (Certainty of evidence: very low).
- Imaging guidance is **conditionally** recommended for use with IAGCs injections of joints that are difficult to access, or to specifically localize the distribution of inflammation. (Certainty of evidence: very low).

1.2.3 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis (2019)

The 2019 ACR/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of JIA-U[8] introduced methods for grading and strength of recommendations, as explained below:

- "A strong recommendation means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation.
- A conditional recommendation means the Voting Panel believed that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation.
- All the recommendations had a very low quality of evidence; thus, most of the recommendations are conditional."

The main recommendations are listed below:

- In children and adolescents with JIA at high risk of developing uveitis, ophthalmic screening every 3 months is **conditionally** recommended over screening at a different frequency.
- In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing topical glucocorticoids, ophthalmic monitoring within 1 month after each change of topical glucocorticoids is **strongly** recommended over monitoring less frequently.
- In children and adolescents with JIA and controlled uveitis on stable therapy, ophthalmic monitoring no less frequently than every 3 months is **strongly** recommended over monitoring less frequently.
- In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing systemic therapy, ophthalmic monitoring within 2 months of changing systemic therapy is **strongly** recommended over monitoring less frequently.
- In children and adolescents with JIA and active chronic anterior uveitis (CAU), using prednisolone acetate 1% topical drops is **conditionally** recommended over difluprednate topical drops.

- In children and adolescents with JIA and active CAU, adding or increasing topical glucocorticoids for short-term control is **conditionally** recommended over adding systemic glucocorticoids.
- In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control, and not on systemic therapy, adding systemic therapy in order to taper topical glucocorticoids is **conditionally** recommended over not adding systemic therapy and maintaining on topical glucocorticoids only.
- In children and adolescents with JIA who develop new CAU activity despite stable systemic therapy, topical glucocorticoids prior to changing/escalating systemic therapy are **conditionally** recommended over changing/escalating systemic therapy immediately.
- In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at least 3 months and on systemic therapy for uveitis control, changing or escalating systemic therapy is **conditionally** recommended over maintaining current systemic therapy.
- In children and adolescents with JIA and CAU who are starting systemic treatment for uveitis, using subcutaneous methotrexate is **conditionally** recommended over oral methotrexate.
- In children and adolescents with JIA with severe active CAU and sight-threating complications, starting methotrexate and a monoclonal antibody TNFi immediately is **conditionally** recommended over methotrexate as monotherapy.
- In children and adolescents with JIA and active CAU, starting a monoclonal antibody TNFi is **conditionally** recommended over etanercept.
- In children and adolescents with JIA and active CAU who have an inadequate response to 1 monoclonal antibody TNFi at standard JIA dose, escalating the dose and/ or frequency to above standard is **conditionally** recommended over switching to another monoclonal antibody TNFi.
- In children and adolescents with JIA and active CAU who have failed a first monoclonal antibody TNFi at above-standard dose and/or frequency, changing to another monoclonal antibody TNFi is **conditionally** recommended over a biologic in another category.
- In children and adolescents with JIA and active CAU who have failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency, the use of abatacept or tocilizumab as biologic DMARD options, and mycophenolate, leflunomide, or cyclosporine as alternative nonbiologic DMARD options is **conditionally** recommended.

- In children and adolescents with spondyloarthritis, **strongly** recommend education regarding the warning signs of acute anterior uveitis (AAU) for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis.
- In children and adolescents with spondyloarthritis otherwise well **controlled** with systemic immunosuppressive therapy (DMARDs, biologics) who develop AAU, **conditionally** recommend against switching systemic immunosuppressive therapy, until treatment with topical corticosteroids has been tried first.

1.2.4 Childhood Arthritis and Rheumatology Research Alliance (CARRA) Consensus Treatment Plans for Juvenile Idiopathic Arthritis-Associated and Idiopathic Chronic Anterior Uveitis (2019)

The main points of CARRA consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis (2019)[9] are detailed below:

- The CARRA formulated consensus treatment plans (CTPs) for CAU with the aim of minimizing differences in practice approaches and enabling future assessments of treatments through comparative effectiveness analysis methods.
- The initial CTP is designed for children who have not yet been exposed to steroid-sparing medications, while the second one is intended for children beginning biologic therapy, offering choices including methotrexate, adalimumab (ADA), and infliximab.
- Patients with CAU who have not been treated with steroid-sparing therapy can benefit from the MTX CTP. While many experts favor subcutaneous MTX due to its higher bioavailability, there is insufficient evidence to confirm its superior efficacy. Surveys of pediatric rheumatologists reveal that both oral and subcutaneous routes are utilized equally. Hence, both methods are viable options for MTX treatment. The recommended MTX dosage is 0.5-1 mg/kg per week, capped at a maximum of 30 mg weekly, with a preference for doses closer to 1 mg/kg/week.
- Patients who do not respond to MTX treatment should be evaluated for the TNFi CTP using monoclonal antibody TNFi. If patients can tolerate MTX, TNFi should be added alongside MTX rather than replacing it. The TNFi CTP may also be an option for MTX-naïve patients with uncontrolled uveitis and severe disease, such as structural complications from uveitis or complications from topical steroid therapy. Simultaneously, MTX treatment, either oral or subcutaneous, from MTX CTP should be initiated.

- There was unanimous agreement that etanercept has no role in the treatment of pediatric uveitis, and that there is insufficient data to recommend either adalimumab or infliximab as the preferred agent.
- The TNFi CTP includes three treatment options: 1) adalimumab SQ injections weekly, 2) adalimumab SQ injections every other week, and 3) infliximab infusions every 4 weeks after loading.
- **MTX intolerance:** The management recommendations for addressing MTX intolerance were deemed outside the scope of these CTPs. The workgroup highlights that methods such as anti-emetics, folic acid, and/or leucovorin use, along with dosage adjustments, can often effectively address MTX intolerance. However, children facing MTX intolerance could also be candidates for the TNFi CTP.
- Systemic Steroids: The workgroup recognized that decisions regarding the administration and dosage of systemic and topical corticosteroids are generally determined by ophthalmologists rather than rheumatologists. Consequently, this CTP does not provide corticosteroid guidance. Nevertheless, expert consensus suggests avoiding systemic steroids for treating CAU. Systemic steroids should only serve as a temporary solution while awaiting the effectiveness of steroid-sparing treatment, and their tapering should commence within two weeks of initiating a steroid-sparing agent.
- There is insufficient data to recommend treatment of uveitis refractory to MTX and TNFi.

1.2.5 The Portuguese Society of Ophthalmology Joint Guidelines with Paediatric Rheumatology on the Screening, Monitoring and Medical Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis (2021)

The main points of the 2021 Portuguese Society of Ophthalmology joint guidelines with Paediatric Rheumatology on the screening, monitoring and medical treatment of JIA-U[5] are detailed below:

Screening, monitoring and medical treatment of JIA-U

The ongoing monitoring and care of these patients needs to be approached in a collaborative manner, involving a multidisciplinary team. An effective partnership between a skilled ophthalmologist and a pediatric rheumatologist is essential, with shared duties and a close working relationship.

- A complete set of clinical data should be documented in the patient's record.

- Pediatric patients who have idiopathic chronic anterior uveitis and test positive for anti-nuclear antibody (ANA) but do not have a confirmed diagnosis of JIA should receive similar management as those with uveitis associated with JIA.
- Screening for uveitis should be initiated in all children as soon as there is suspicion or investigation of JIA, rather than delaying until the disease is definitively confirmed.
- When conducting ophthalmological screening for JIA patients, the slit lamp examination is obligatory.
- The screening schedule for these children should be adjusted based on their likelihood of developing uveitis.
- Regular screening is necessary for both children with ongoing uveitis activity and those with inactive uveitis who are undergoing a reduction in immunosuppressive treatment.
- Children with active uveitis and children with inactive uveitis in whom immunosuppressive treatment is being de-escalated should be screened regularly.
- Initiation of treatment for anterior uveitis should commence when there are ≥0.5 AC cells.
- For active uveitis, primary treatment with high-potency topical steroids is recommended. These should be administered initially in a concentrated burst, followed by a gradual reduction in dosage.
- When there is evident inflammatory activity (0.5 cells or higher in the anterior chamber), cycloplegics should be included in the treatment regimen.
- In cases of complex disease or when sight-threatening complications are present, systemic steroids should be contemplated to swiftly manage inflammation.
- Extended administration of systemic steroids should be minimized to prevent potential adverse outcomes.
- For children who do not adequately respond to topical steroids or exhibit substantial structural complications, the commencement of immunosuppressive treatment should not be postponed.
- In patients who do not respond well to topical steroids or who have notable structural complications, MTX should be employed as the initial treatment option. Additionally, consistent monitoring for potential adverse effects should be conducted.

- In the case of JIA-U, the preferred initial biologic medication is ADA.
- When advancing to ADA treatment, it is advisable to continue with MTX unless there are contraindications or adverse reactions.
- Continuous monitoring of long-term MTX and ADA treatment should be carried out by a pediatric rheumatologist.
- Etanercept is contraindicated for children with JIA-U and should be steered clear of when addressing joint symptoms of JIA in individuals with a uveitis history.
- If there are indications of inadequate response to ADA (such as insufficient inflammation control or repeated use of topical steroids for recurring/persistent uveitis), it is advisable to assess ADA serum levels, ascertain the presence of neutralizing antibodies, and reevaluate the treatment approach.
- If the joint use of MTX and ADA fails to effectively manage ocular inflammation, the option of transitioning treatment to infliximab, tocilizumab, abatacept, or rituximab should be considered.
- The possibility of reducing or discontinuing immunosuppressants may be contemplated following a period of 2 years without uveitis activity.
- The use of periocular or intravitreal steroids should only be contemplated for JIA-U instances that do not respond to optimized systemic treatment or involve severe complications jeopardizing vision.
- In cases where ocular surgery is required, such as for cataract or glaucoma, the administration of perioperative supplementary treatment (which may involve systemic and topical steroids) should be meticulously coordinated between the ophthalmologist and pediatric rheumatologist.
- Families and, if of appropriate age, patients themselves should receive comprehensive information regarding the potential occurrence of uveitis in JIA.
- Active involvement of both the patient and their family in collaborative care, including discussions about follow-up, treatment approaches, and prognosis, is of utmost importance.
- Additional conventional immunosuppressive medications (like mycophenolate mofetil, azathioprine, or cyclosporine) could be considered if there are contraindications, intolerance, or toxicity associated with MTX. However, there isn't sufficient evidence to firmly establish any of these drugs as definitive second-line treatments for rescuing patient’s refractory to MTX.

Section 2.0 Drug Therapy in Juvenile Idiopathic Arthritis

This section comprises three subsections: the first contains the newly recommended drugs, the second covers drug modifications, and the third outlines the drugs that have been withdrawn from the market.

2.1 Additions

- **Kineret (anakinra)** was approved by the European Medicines Agency (EMA) for the treatment of systemic and polyarticular course JIA on August 3, 2002. (SFDA registered)
- U.S. FDA Approves Pfizer's **Xeljanz (tofacitinib)** for the Treatment of Active Polyarticular Course JIA on Sep 28,2020. (SFDA registered)
- **Simponi Aria (golimumab)** obtained FDA approval in 2020 for its indication in the pediatric population on treating active polyarticular JIA and psoriatic arthritis in patients aged two years and above. (SFDA registered)

2.1.1 Anakinra

This section includes pertinent information regarding the use of Anakinra (KINERET®) in systemic and polyarticular course JIA[10]:

Table 4. Drug Therapy with Anakinra

SCIENTIFIC NAME **Anakinra**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	No
EMA	Yes
MHRA	Yes
PMDA	No
Indication (ICD-10)	M08
Drug Class	Antirheumatic, Disease Modifying
Drug Sub-class	Interleukin-1 Receptor Antagonist
ATC Code	L04AC03
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Solution for injection

Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	N/A
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**JIA:** Limited data available: - **Systemic JIA:** Children and Adolescents: SubQ: Initial: 1 to 2 mg/kg/dose once daily; maximum initial dose: 100 mg; if no response, may titrate typically at 2-week intervals by doubling dose up to 4 mg/kg/dose once daily; maximum dose: 200 mg. - **Polyarticular course JIA:** Children ≥2 years and Adolescents: SubQ: 1 mg/kg once daily; maximum dose: 100 mg
Maximum Daily Dose Pediatrics*	- **Systemic JIA:** maximum dose: 200 mg - **Polyarticular course JIA:** maximum dose: 100 mg
Adjustment	<u>Altered kidney function:</u> - CrCl ≥30 mL/minute: No dosage adjustment necessary - CrCl <30 mL/minute: I. Deficiency of interleukin-1 receptor antagonist (DIRA), neonatal-onset multisystem inflammatory disease (NOMID) (cryopyrin-associated periodic syndromes [CAPS]; chronic infantile neurological, cutaneous, and articular syndrome [CINCA]): Infants, Children, and Adolescents: Decrease frequency of administration to every other day. II. Rheumatoid arthritis: Adolescents ≥18 years: Consider 100 mg every other day.

	- End-stage renal disease: <2.5% of the dose is removed by hemodialysis or CAPD: I. Deficiency of interleukin-1 receptor antagonist (DIRA), neonatal-onset multisystem inflammatory disease (NOMID) (cryopyrin-associated periodic syndromes [CAPS]; chronic infantile neurological, cutaneous, and articular syndrome [CINCA]): Infants, Children, and Adolescents: Decrease frequency of administration to every other day. II. Rheumatoid arthritis: Adolescents ≥18 years: 100 mg every other day. <u>Hepatic impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	PA, MD, ST
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a rheumatologist.	
PA (Prior Authorization): This medication is expensive, needs to be prescribed by a rheumatologist and is recommended when other treatment options have failed.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Anakinra could be considered for children diagnosed with systemic JIA who have not shown improvement when treated with systemic corticosteroids (while displaying active systemic features) or methotrexate (when experiencing active arthritis) or associated with MAS.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	<u>Most common:</u>

	Increased gamma-glutamyl transferase, increased serum transferase, vomiting, antibody development, infection, injection site reaction, headache, arthralgia nasopharyngitis, fever Most serious: Anaphylaxis/hypersensitivity reactions, infections, injection site reactions, malignancy, neutropenia
Drug Interactions	**Category X:** • Abatacept • Abrocitinib • ADA • Adenovirus (Types 4, 7) Vaccine • Anifrolumab • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine • Canakinumab • Certolizumab Pegol • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Etanercept • Filgotinib • Golimumab • Infliximab • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Lenalidomide • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine

	• Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Pomalidomide • Ritlecitinib • Rituximab • Rotavirus Vaccine • Ruxolitinib (Topical) • Sarilumab • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Thalidomide • Tocilizumab • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated)
Special Population	N/A
Pregnancy	Until additional data are available, anakinra is not currently recommended for the treatment of rheumatic and musculoskeletal diseases during pregnancy. Anakinra should be discontinued once pregnancy is confirmed.
Lactation	It is not known if anakinra is present in breast milk. Adverse events have not been observed in breastfeeding infants following maternal use of anakinra. According to

	the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Concentrations of anakinra are expected to be limited in breast milk due to large molecular weight. Also, because anakinra is unlikely to be absorbed by the infant gastrointestinal tract following exposure via breast milk, treatment with anakinra may be initiated in breastfeeding patients with rheumatic and musculoskeletal diseases.
Contraindications	Hypersensitivity to E. coli-derived proteins, anakinra, or any component of the formulation
Monitoring Requirements	Monitor CBC with differential (baseline, then monthly for 3 months, then every 3 months for a period up to 1 year); TB test (baseline); serum creatinine; signs/symptoms of infection; injection site reactions.
Precautions	- Asthma: Use with caution in patients with asthma; may have increased risk of serious infection. - Renal impairment: Use caution in patients with renal impairment. - TNFi: Anakinra should not be initiated in patients receiving TNFi (eg, etanercept) due to increased risk of serious infection.
Black Box Warning	N/A
REMS	N/A

Clinical Trials – Anakinra

A multicenter, randomized, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-JIA (ANAJIS trial) was conducted to evaluate the efficacy of the IL-1 receptor antagonist anakinra in treating systemic JIA[11].

The main goal was to contrast the effectiveness of a one-month therapy using anakinra (at a daily subcutaneous dose of 2 mg/kg, up to a maximum of 100 mg) against a placebo. This comparison was conducted between two groups, each consisting of 12 patients with systemic JIA. A positive response was defined as achieving a 30% improvement based on the pediatric ACR criteria for JIA, along with the resolution of systemic symptoms and a reduction of at least 50% in both C-reactive protein and erythrocyte sedimentation rate when compared to the baseline measurements[11].

"Inclusion criteria were age 2–20 years, a diagnosis of systemic JIA, 1 more than 6 months' disease duration, active systemic disease (disease-related fever and/ or C-reactive protein (CRP) >20 mg/l and/or first hour erythrocyte sedimentation rate (ESR) >20) and significant overall disease activity at day 1 (D1) (at least three of the following criteria: (1) physician global assessment of disease activity ≥20/100; (2) parent/patient assessment of disease effect on overall wellbeing ≥20/100; (3) Childhood Health Assessment Questionnaire score ≥0.375/3; (4) ≥2 joints with active arthritis; (5) ≥2 joints with non-irreversible limited range of motion and (6) ESR ≥30) despite oral prednisone or prednisolone ≥0.3 mg/kg or 10 mg/day (whichever was lower)"[11].

Based on the trial's results, the use of anakinra therapy demonstrated effectiveness in addressing systemic JIA, particularly in the immediate term. This treatment showed to be linked with the restoration of typical blood gene expression patterns among those who respond well clinically, and it triggers the formation of a new interferon (IFN) signature[11].

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of JIA treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for anakinra.**

Table 5. Anakinra HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Anakinra	NICE[12]	03/2021: The panel recognized the requirement for biological treatment alternatives for individuals with Still's disease. It found the economic model provided by the company unfit for making decisions. Nonetheless, it determined that the cost-minimization analysis indicated that anakinra and tocilizumab have comparable weekly expenses. As a result, anakinra is suggested as a choice for: - Systemic JIA when there hasn't been a positive response to at least one conventional disease-modifying antirheumatic drug (DMARD). - Adult-onset Still's disease when there's been an insufficient response to two or more conventional DMARDs.
	CADTH[13]	Submission temporarily suspended
	HAS[14]	03/2019: Prominent clinical advantages are observed in both pediatric and adult cases of Still's disease, although no discernible clinical benefits are shown in the overall management approach. KINERET has been granted Marketing Authorization for the treatment of Still's disease, specifically for systemic JIA and adult-onset Still's disease (ASM). This authorization applies to individuals aged 8 months and above, weighing at least 10 kg, who have active systemic manifestations of moderate to severe intensity or persistent activity after treatment with NSAIDs or corticosteroids.
	IQWIG	N/A
	PBAC[15]	"This drug is not PBS-subsidized for conditions other than cryopyrin-associated autoinflammatory syndromes (CAPS)"

Conclusion Statement – Anakinra

Anakinra showed to be effective in the treatment of systemic JIA in children who have failed to respond to systemic corticosteroids, conventional DMARDs or MTX.

It is important to note that there is conflicting data or recommendations from HTA bodies regarding the use of anakinra for the management of systemic JIA. NICE and HTA bodies recommend the use of anakinra for the treatment of JIA under certain conditions, whereas the application for CADTH is temporarily suspended and PBS only subsidized conditions for the treatment of cryopyrin-associated autoinflammatory syndromes (CAPS).

2.1.2 Tofacitinib

This section includes pertinent information regarding the use of Tofacitinib (XELJANZ®) in JIA[10].

Table 6. Drug Therapy with Tofacitinib

SCIENTIFIC NAME **Tofacitinib**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	M08
Drug Class	Antirheumatic, Disease Modifying; Antirheumatic, Miscellaneous
Drug Sub-class	Janus Kinase Inhibitor
ATC Code	L04AA29
Pharmacological Class (ASHP)	92:36 - Disease-modifying Antirheumatic Agents
DRUG INFORMATION	
Dosage Form	Modified-release tablet
Route of Administration	Oral use
Dose (Adult) [DDD]*	N/A
Maximum Daily Dose Adults*	N/A

Dose (pediatrics)	**JIA, polyarticular course**: Children ≥2 years weighing ≥10 kg and Adolescents: Oral: 10 to <20 kg: Oral solution (1 mg/mL): 3.2 mg twice daily. 20 to <40 kg: Oral solution (1 mg/mL): 4 mg twice daily. ≥40 kg: Oral solution (1 mg/mL) or immediate-release tablet: 5 mg twice daily.
Maximum Daily Dose Pediatrics*	5 mg twice daily
Adjustment	<u>Altered kidney function:</u> Children ≥2 years and Adolescents: Oral: Oral solution, immediate-release tablets: - Mild kidney impairment: No adjustment necessary. - Moderate to severe kidney impairment: Reduce dose frequency to once daily. - Hemodialysis: Administer dose after dialysis session on dialysis days; if dose administered before session, a supplemental dose post-dialysis is not recommended. <u>Hepatic impairment:</u> There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).
Prescribing edits*	PA, MD, AGE, ST
AGE (Age Edit): Not to be used in children less than 2 years of age.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a rheumatologist.	
PA (Prior Authorization): This medication is expensive, age specific, needs to be prescribed by a rheumatologist and is usually recommended when other treatment options have failed.	
QL (Quantity Limit): N/A	

ST (Step Therapy): Tofacitinib is often considered after conventional therapies like NSAIDs, DMARDs like methotrexate, and even biologic DMARDs like TNFi have been tried and have not provided sufficient disease control or have led to intolerable side effects.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	<u>Most common:</u> Hyperlipidemia, infection, nasopharyngitis <u>Most serious:</u> Bone marrow suppression, cardiovascular events, GI perforation, GI perforation, hepatic effects, infection, malignancy, thrombosis, tuberculosis
Drug Interactions	**<u>Category X:</u>** - Abatacept - Abemaciclib - Abrocitinib - Acalabrutinib - Adalimumab - Adenovirus (Types 4, 7) Vaccine - Alemtuzumab - Amsacrine - Anakinra - Anifrolumab - Antithymocyte Globulin (Equine) - Antithymocyte Globulin (Rabbit) - Apalutamide - Asciminib - Avacopan - Axicabtagene Ciloleucel - Azacytidine - Azathioprine - Baricitinib - Basiliximab - BCG (Intravesical) - BCG Vaccine (Immunization) - Belatacept

	- Belimumab - Belinostat - Bimekizumab - Blinatumomab - Brentuximab Vedotin - Brexucabtagene Autoleucel - Brivudine - Brodalumab - Busulfan - Cabazitaxel - Canakinumab - Capecitabine - Carbamazepine - Carboplatin - Carfilzomib - Carmustine - Certolizumab Pegol - Chlorambucil - Cholera Vaccine - Ciltacabtagene Autoleucel - Cisplatin - Cladribine - Clofarabine - Copanlisib - Cyclophosphamide - Cyclosporine (Systemic) - Cytarabine (Conventional) - Dacarbazine - Dactinomycin - Daratumumab - Dasatinib - Daunorubicin (Conventional) - Daunorubicin (Liposomal) - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Dinutuximab - Dipyrone - Docetaxel - Doxifluridine

	- Doxorubicin (Conventional) - Doxorubicin (Liposomal) - Duvelisib - Ebola Zaire Vaccine (Live) - Eculizumab - Efgartigimod Alfa - Elivaldogene Autotemcel - Elotuzumab - Emapalumab - Enzalutamide - Epcoritamab - Epirubicin - Etanercept - Etoposide - Etoposide Phosphate - Everolimus - Fexinidazole - Filgotinib - Fingolimod - Floxuridine - Fludarabine - Fluorouracil (Systemic) - Fosphenytoin - Fotemustine - Fusidic Acid (Systemic) - Gemcitabine - Gemtuzumab Ozogamicin - Glofitamab - Golimumab - Guselkumab - Hydroxyurea - Ibritumomab Tiuxetan - Ibrutinib - Idarubicin - Idecabtagene Vicleucel - Idelalisib - Ifosfamide - Imatinib - Inebilizumab

	- Infliximab - Influenza Virus Vaccine (Live/Attenuated) - Inotuzumab Ozogamicin - Irinotecan (Conventional) - Irinotecan (Liposomal) - Isatuximab - Ixabepilone - Ixekizumab - Japanese Encephalitis Virus Vaccine (Live/Attenuated) - Lenalidomide - Lisocabtagene Maraleucel - Lomustine - Loncastuximab Tesirine - Lumacaftor and Ivacaftor - Lurbinectedin - Lutetium Lu 177 Dotatate - Lutetium Lu 177 Vipivotide Tetraxetan - Measles, Mumps, and Rubella Virus Vaccine - Measles, Mumps, Rubella, and Varicella Virus Vaccine - Mechlorethamine (Systemic) - Melphalan - Melphalan Flufenamide - Mercaptopurine - Mitomycin (Systemic) - Mitotane - Mitoxantrone - Mizoribine - Mogamulizumab - Mosunetuzumab - Mumps Virus Vaccine - Mycophenolate - Nadofaragene Firadenovec - Natalizumab - Nelarabine

	- Niraparib - Obinutuzumab - Ocrelizumab - Ofatumumab - Omacetaxine - Ozanimod - Paclitaxel (Conventional) - Paclitaxel (Protein Bound) - Pacritinib - Palbociclib - Panobinostat - Pazopanib - Pegcetacoplan (Systemic) - Pemetrexed - Pentostatin - Phenobarbital - Phenytoin - Pimecrolimus - Pirtobrutinib - Pixantrone - Polatuzumab Vedotin - Poliovirus Vaccine (Live/Bivalent/Oral) - Poliovirus Vaccine (Live/Trivalent/Oral) - Pomalidomide - Ponatinib - Ponesimod - Pralatrexate - Primidone - Procarbazine - Raltitrexed - Ravulizumab - Ribociclib - Rifampin - Rilonacept - Risankizumab - Ritlecitinib - Rituximab

	- Romidepsin - Rotavirus Vaccine - Rozanolixizumab - Ruxolitinib (Systemic) - Ruxolitinib (Topical) - Sacituzumab Govitecan - Sarilumab - Satralizumab - Secukinumab - Selinexor - Siltuximab - Siponimod - Sirolimus (Conventional) - Sirolimus (Protein Bound) - Sirolimus (Topical) - Smallpox Vaccine Live - Spesolimab - Sutimlimab - Tacrolimus (Systemic) - Tacrolimus (Topical) - Tafasitamab - Talimogene Laherparepvec - Tazemetostat - Teclistamab - Tegafur - Temozolomide - Temsirolimus - Teniposide - Teplizumab - Tertomotide - Thioguanine - Thiotepa - Tisagenlecleucel - Tocilizumab - Trabectedin - Treosulfan - Trifluridine and Tipiracil - Typhoid Vaccine - Ublituximab

	- Umbralisib - Upadacitinib - Ustekinumab - Varicella Virus Vaccine - Vedolizumab - Venetoclax - Vilobelimab - Vinblastine - Vinflunine - Vinorelbine - Voclosporin - Yellow Fever Vaccine - Zanubrutinib - Zoster Vaccine (Live/Attenuated)
Special Population	N/A
Pregnancy	Outcome data following tofacitinib exposure in pregnancy are limited. Recommendations for use of tofacitinib in pregnant patients with rheumatic and musculoskeletal diseases are not available due to lack of data. Placental transfer may be expected based on molecular weight.
Lactation	It is not known if tofacitinib is present in breast milk. Recommendations for use of tofacitinib in breastfeeding patients with rheumatic and musculoskeletal diseases are not available due to lack of data. Transfer into breast milk may be expected based on molecular weight. Tofacitinib is not recommended to treat inflammatory bowel disease in patients who are breastfeeding. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer does not recommend breastfeeding during treatment and for at least 18 hours after the last dose of immediate release tofacitinib or 36 hours (~6 half-

	lives) after the last dose of tofacitinib extended release.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Hypersensitivity to tofacitinib or any component of the formulation; severe hepatic impairment; pregnancy; breastfeeding.
Monitoring Requirements	Monitor Lymphocyte count (baseline and every 3 months thereafter); neutrophil/platelet counts (baseline, after 4 to 8 weeks, and every 3 months thereafter); hemoglobin (baseline, after 4 to 8 weeks, and every 3 months thereafter); lipids (4 to 8 weeks after therapy initiation and periodically); LFTs; viral hepatitis (prior to initiating therapy in accordance with clinical guidelines); signs/symptoms of infections (including tuberculosis) during and after therapy; abdominal symptoms; skin examinations (periodically, in patients at increased risk for skin cancer); heart rate and blood pressure at baseline and periodically thereafter.
Precautions	***Concerns related to adverse effects:*** • Hypersensitivity: Hypersensitivity reactions, including angioedema and urticaria, have occurred; discontinue therapy and evaluate cause for serious reactions. • Interstitial lung disease: Interstitial lung disease (ILD) has been reported; patients developing ILD were receiving concomitant therapy associated with ILD (eg, MTX). Use with caution in patients with risk/history of ILD (Xeljanz

	Canadian product monograph). ***Disease-related concerns:*** • Active infections: Do not initiate tofacitinib in patients with active infections, including localized infections. • Hepatic impairment: Use with caution in patients with hepatic impairment; see "Dosing: Hepatic Impairment" for additional information. • Lung disease: Patients with a history of chronic lung disease or those who develop interstitial lung disease may be more prone to infections; use with caution. • Renal impairment: Use with caution in patients with renal impairment; see "Dosing: Altered Kidney Function" for additional information. ***Concurrent drug therapy issues:*** • Immunosuppressant medications: Tofacitinib should not be administered in combination with strong immunosuppressive medications (eg, azathioprine, tacrolimus, cyclosporine) due to the risk of additive immunosuppression; such combinations have not been studied in RA. • Biologic DMARDs: Tofacitinib should not be administered in combination with biologic DMARDs
Black Box Warning	Serious infections such as active tuberculosis (TB), invasive fungal

	infections, bacterial, viral (including herpes zoster), mortality, malignancies, major adverse cardiovascular events, thrombosis
REMS	N/A

Clinical Trials – Tofacitinib

A double-blind, placebo-controlled, withdrawal phase 3 randomized trial was conducted to evaluate the efficacy and safety of tofacitinib versus placebo in patients with polyarticular course juvenile idiopathic arthritis (JIA)[16].

Children aged 2 to under 18 years, diagnosed with polyarticular course JIA, which includes extended oligoarthritis, rheumatoid factor-positive or -negative polyarthritis, or systemic JIA without active systemic features, were included in the study. The research was carried out across 64 centers spanning 14 countries, all of which were part of the networks of the Paediatric Rheumatology International Trials Organisation and the Pediatric Rheumatology Collaborative Study Group[16].

The study consisted of two phases: in the first phase, patients with polyarticular course JIA received oral open-label tofacitinib (weight-based doses; 5 mg twice daily or lower) for 18 weeks. Those achieving a JIA/ACR 30 response were randomly assigned to either continue tofacitinib or switch to a placebo for the second phase lasting 26 weeks. The primary focus was on JIA flare rates by week 44 in the second phase among polyarticular JIA patients, with adherence to the intention-to-treat principle[16].

Between June 10, 2016, and May 16, 2019, a total of 225 enrolled patients were categorized: 184 (82%) with polyarticular course JIA, 20 (9%) with psoriatic arthritis, and 21 (9%) with enthesitis-related arthritis. Among them, 147 (65%) received MTX alongside their treatment. In the second phase of the study, 142 patients with polyarticular JIA were divided into two groups, with 72 receiving tofacitinib and 70 receiving a placebo. The flare rate by week 44 was notably lower in the tofacitinib group (29%) compared to the placebo group (53%), with a significant difference in favor of tofacitinib (hazard ratio 0.46). In part 2, adverse events were observed in 77% of those on tofacitinib and 74% of those on placebo, with serious adverse events occurring in 1% and 2%, respectively. Throughout the tofacitinib treatment period, infections or infestations were reported in 48% of patients. No deaths occurred during the study[16].

The outcomes of this pivotal trial demonstrate that tofacitinib proves to be a successful therapy for individuals with polyarticular JIA. Oral treatments like tofacitinib are especially significant for young patients as they might wish to avoid injections, which is particularly relevant for children and adolescents[16].

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of JIA treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for tofacitinib.**

Table 7. Tofacitinib HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Tofacitinib	NICE[17]	10/2021: Tofacitinib can be considered as a viable treatment option for managing active polyarticular JIA – encompassing both rheumatoid factor positive or negative polyarthritis and extended oligoarthritis – as well as juvenile psoriatic arthritis in individuals aged 2 years and older. This recommendation applies when prior treatment with DMARDs has yielded inadequate results. However, it should only be considered: - if the use of a TNFi is not feasible or has not effectively controlled the condition, and - provided that the pharmaceutical company offers tofacitinib as part of the established commercial agreement.
	CADTH	N/A for this indication
	HAS[18]	06/2022: Supportive opinion for reimbursement for the management of active polyarticular JIA including both rheumatoid factor positive (RF+) or negative (RF-) arthritis and extended oligoarthritis, as well as juvenile psoriatic arthritis in individuals aged 2 years and older. Furthermore, this endorsement applies to cases where there has been an insufficient response to previous DMARD treatments. Tofacitinib can be used either alongside MTX or as a standalone treatment option in instances of MTX intolerance or when ongoing MTX usage is deemed unsuitable.
	IQWIG[19]	12/2021: There is insufficient data to evaluate the extra advantages of tofacitinib versus the appropriate comparator therapy (ACT) in individuals with active polyarticular JIA and juvenile psoriatic arthritis, aged 2

		years and older, who have not adequately responded to prior DMARDs treatment. Consequently, there is no indication of enhanced benefits from tofacitinib over the ACT, and as such, the proof of additional benefits is not established.
	PBAC	N/A for this indication

Conclusion Statement – Tofacitinib

Tofacitinib is considered for the treatment of JIA, specifically for cases where other treatments have not been effective or have been poorly tolerated.

It is important to note that there is conflicting data or recommendations from HTA bodies regarding the use of tofacitinib for the management of systemic JIA. NICE and HAS bodies concluded that the use of tofacitinib is effective in the management of JIA under specific conditions, however IQWIG deduced that there is no sufficient data to assess the added benefit of tofacitinib versus the conventional treatment.

2.1.3 Golimumab

This section includes pertinent information regarding the use of Golimumab (SIMPONI®) in JIA[20]:

Table 8. Drug Therapy with Golimumab

SCIENTIFIC NAME **Golimumab**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Not for this indication
PMDA	Not for this indication
Indication (ICD-10)	M08
Drug Class	Antipsoriatic Agent; Antirheumatic, Disease Modifying; Monoclonal Antibody
Drug Sub-class	TNF Blocking Agent
ATC Code	L04AB06
Pharmacological Class (ASHP)	92:20 - Biologic Response Modifiers; 92:36 - DMARDs

DRUG INFORMATION	
Dosage Form	Solution for injection in pre-filled pen
Route of Administration	Subcutaneous use
Dose (Adult) [DDD]*	N/A
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	**JIA, polyarticular:** 30mg/m2 of body surface area; maximum: 50mg/dose) every 4 weeks together with weekly MTX
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Altered kidney function: There are no dosage adjustments provided in manufacturer's labeling (has not been studied). Hepatic impairment: There are no dosage adjustments provided in manufacturer's labeling (has not been studied).
Prescribing edits*	ST, PA, CU
AGE (Age Edit): Not to be used in children less than 2 years of age.	
CU (Concurrent Use Edit): Should be used with MTX.	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Should be prescribed by a rheumatologist.	
PA (Prior Authorization): This medication is expensive, age specific, needs to be prescribed by a rheumatologist, should be used concurrently with another medication, and is usually recommended when other treatment options have failed.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Golimumab is often used when a child or adolescent with JIA has not responded adequately to conventional DMARDs or other biologic DMARDs, such as TNFi.	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	Most common: Positive ANA titer, antibody development, infection, upper respiratory tract infection

	Most serious: Hypersensitivity angiitis, septic shock, vasculitis, leukemia, septic arthritis, hepatotoxicity, agranulocytosis, aplastic anemia, malignant lymphoma, malignant melanoma, malignant neoplasm, Merkel cell carcinoma, neutropenia, pancytopenia, sarcoidosis, thrombocytopenia, Lupus-like syndrome, multiple sclerosis, demyelinating disease of the central nervous system, Guillain-Barre syndrome, peripheral demyelinating polyneuropathy, optic neuritis
Drug Interactions	**Category X:** - Abatacept - Abrocitinib - ADA - Adenovirus (Types 4, 7) Vaccine - Anakinra - Anifrolumab - Baricitinib - BCG (Intravesical) - BCG Vaccine (Immunization) - Brivudine - Canakinumab - Certolizumab Pegol - Cholera Vaccine - Cladribine - Dengue Tetravalent Vaccine (Live) - Deucravacitinib - Ebola Zaire Vaccine (Live) - Etanercept - Filgotinib - Infliximab - Influenza Virus Vaccine (Live/Attenuated) - Japanese Encephalitis Virus Vaccine (Live/Attenuated)

	- Measles, Mumps, and Rubella Virus Vaccine - Measles, Mumps, Rubella, and Varicella Virus Vaccine - Mumps Virus Vaccine - Nadofaragene Firadenovec - Natalizumab - Pimecrolimus - Poliovirus Vaccine (Live/Bivalent/Oral) - Poliovirus Vaccine (Live/Trivalent/Oral) - Rilonacept - Ritlecitinib - Rituximab - Rotavirus Vaccine - Ruxolitinib (Topical) - Sarilumab - Smallpox Vaccine Live - Tacrolimus (Topical) - Talimogene Laherparepvec - Tertomotide - Tocilizumab - Tofacitinib - Typhoid Vaccine - Upadacitinib - Varicella Virus Vaccine - Vedolizumab - Yellow Fever Vaccine - Zoster Vaccine (Live/Attenuated)
Special Population	Pediatric: [US Boxed Warning]: Lymphoma and other malignancies (some fatal) have been reported in children and adolescent patients receiving TNFi.
Pregnancy	- Golimumab crosses the placenta. - Placental transfer of human IgG is dependent upon the IgG subclass, maternal serum

	concentrations, birth weight, and gestational age, generally increasing as pregnancy progresses. The lowest exposure would be expected during the period of organogenesis. - Information related to this class of medications is emerging, but based on available data, tumor necrosis factor alpha (TNFα) blocking agents are considered to have low to moderate risk when used in pregnancy. - Use of immune modulating therapies in pregnancy should be individualized to optimize maternal disease and pregnancy outcomes
Lactation	It is not known if golimumab is present in breast milk. Breast milk was sampled in one woman for up to 7 days following golimumab injection. Golimumab was not detected in any of the samples. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother. However, tumor necrosis factor alpha (TNFα) blocking agents are considered compatible with breastfeeding.
Contraindications	There are no contraindications listed in the manufacturer's US labeling. Canadian labeling: Hypersensitivity to golimumab, latex, or any other component of formulation or packaging; patients with severe infections (eg, sepsis, tuberculosis,

	opportunistic infections); moderate or severe heart failure (NYHA class III/IV).
Monitoring Requirements	Monitor CBC with differential; latent tuberculosis screening (prior to initiating and periodically during therapy); hepatitis B virus (HBV) screening (prior to initiating [all patients]; during and for several months following therapy [HBV carriers]); hepatitis C virus screening. If clinically appropriate, may consider antidrug antibody testing; refer to clinical guidelines. Monitor improvement of symptoms and physical function assessments. Monitor for signs/symptoms of demyelinating disease, heart failure (including worsening heart failure), hypersensitivity reaction, infection (prior to, during, and following therapy), and lupus-like syndrome. Monitor for signs/symptoms of malignancy (eg, splenomegaly, hepatomegaly, abdominal pain, persistent fever, night sweats, weight loss) including periodic skin examination.
Precautions	- Autoimmune disorder: Positive ANA titers have been detected in patients (with negative baselines). Rare cases of autoimmune disorder, including lupus-like syndrome, have been reported; monitor and discontinue if symptoms develop. - Demyelinating disease: rare cases of new-onset or exacerbation of demyelinating disorders (eg, multiple sclerosis, optic neuritis, Guillain-Barré syndrome, polyneuropathy) have been reported. Consider discontinuing in patients who develop peripheral or CNS

	demyelinating disorders during treatment. Use with caution in patients with pre-existing or recent onset central or peripheral nervous system demyelinating disorders. - Heart failure: Worsening and new-onset heart failure (HF) (some fatal) have been reported with golimumab and other TNF-blockers. Monitor closely and discontinue with onset or worsening of symptoms. Use with caution in patients with HF or decreased left ventricular function. In a scientific statement from the American Heart Association, TNF blockers have been determined to be agents that may either cause direct myocardial toxicity or exacerbate underlying myocardial dysfunction (magnitude: major). - Hematologic effects: Cases of pancytopenia and other significant cytopenias, including aplastic anemia, have been reported with TNFi. Pancytopenia, leukopenia, neutropenia, and thrombocytopenia have occurred with golimumab. Consider discontinuing with significant hematologic abnormalities. Use with caution in patients with underlying hematologic disorders. - Hepatitis B: Rare reactivation of hepatitis B virus (HBV), sometimes fatal, has occurred in chronic virus carriers, usually in patients receiving concomitant immunosuppressants; evaluate for HBV prior to initiation in all patients. Patients who test positive for HBV surface antigen should be referred for hepatitis B

	evaluation/treatment prior to golimumab initiation. Monitor for clinical and laboratory signs of active infection during and for several months following discontinuation of golimumab treatment in HBV carriers; interrupt therapy if reactivation occurs and treat appropriately with antiviral therapy; if resumption of therapy is deemed necessary, exercise caution and monitor patient closely. - Hypersensitivity reactions: Severe systemic hypersensitivity reactions (including anaphylaxis) have been reported (some have occurred with the first dose) following intravenous and subcutaneous administration. Symptoms associated with reactions may include dyspnea, hives, nausea, and pruritus; reactions occurred during and within 1 hour of the start of IV infusion. Discontinue immediately if signs develop and initiate appropriate treatment.
Black Box Warning	- Serious infections including Active tuberculosis (TB), invasive fungal infections, bacterial, viral, and other infections due to opportunistic pathogens, including Legionella and Listeria - Lymphoma and other malignancies
REMS	N/A

<u>Clinical Trials – Golimumab</u>

A multicenter, double-blind, randomized withdrawal trial was conducted to assess the safety, pharmacokinetics (PK) and efficacy of subcutaneous golimumab in active polyarticular-course JIA.

Patients aged between 2 and 17 years, diagnosed with various forms of JIA including rheumatoid factor (RF)-positive or RF-negative polyarticular, extended oligoarticular

JIA, systemic JIA without systemic features, and juvenile psoriatic arthritis, were eligible for the study. The requirement was that the patients should have had active JIA with at least 5 affected joints, characterized by joint swelling or, in cases without swelling, limited range of motion (LROM) combined with pain during movement and/or tenderness upon palpation. Despite having received MTX treatment for a minimum of 3 months (with dosages ranging from 10 to 30 mg/m^2/week, or ≥15 mg/week for those with a body surface area ≥1.67), the patients' JIA remained active. The study had a mandate that 80% of enrolled patients should not have been previously treated with biologic disease-modifying antirheumatic drugs (DMARDs), while the remaining patients could have encountered failure with a maximum of one TNFi.

In this randomized, double-blind, placebo-controlled withdrawal trial conducted in three parts, all patients were initially treated with open-label golimumab at a dose of 30mg/m^2 of body surface area (with a maximum of 50mg per dose) every 4 weeks, in addition to weekly MTX during the first phase (weeks 0–16). Patients who achieved a minimum of 30% improvement according to the ACR Criteria for JIA ACR30 during this initial phase proceeded to the second phase (weeks 16–48), where they were randomly assigned to either continue with golimumab or start receiving a placebo at a 1:1 ratio. In the third phase, golimumab treatment was maintained or could be restarted as in the initial phase (Part 1). The primary focus was on JIA flares during the second phase, with additional secondary outcomes encompassing JIA ACR50/70/90 responses, clinical remission, pharmacokinetics, and safety assessments.

Out of the 173 enrolled patients with polyarticular JIA a significant proportion, accounting for 89.0% (154 out of 173), achieved a JIA ACR30 response in Part 1 of the study. Moreover, proportions of 79.2%, 65.9%, and 36.4% demonstrated JIA ACR50, ACR70, and ACR90 responses, respectively. However, by week 48, the primary objective was not met, as there were comparable JIA flare rates between treatment groups (41% for golimumab vs. 47% for placebo; p=0.41), along with similar rates of clinical remission (12.8% for golimumab vs. 11.8% for placebo). During Part 2, adverse events and serious adverse events occurred at similar rates in both treatment groups. Incidences of injection site reactions were reported in less than 1% of all injections. Pharmacokinetic (PK) analysis affirmed that golimumab dosing for polyarticular JIA was appropriate.

Even though the primary endpoint was not reached, golimumab led to a clinically significant enhancement in the condition of children dealing with active polyarticular JIA. Golimumab's tolerability was satisfactory, and there were no unforeseen safety incidents reported.

Health Technology Assessment (HTA)

The table below lists the HTA reviews and recommendations of juvenile idiopathic arthritis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for golimumab.**

Table 9. Golimumab HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Golimumab	NICE	N/A
	CADTH	N/A
	HAS	02/2019: The clinical benefits observed are not substantial enough to warrant reimbursement for polyarticular JIA.
	IQWIG	N/A
	PBAC	N/A for this indication

Conclusion Statement – Golimumab

Golimumab was shown to be effective for the treatment of JIA in cases where other treatments have not been effective or are poorly tolerated. It is generally considered when the JIA is characterized by moderate to severe disease activity and when other DMARDs or biologic agents have not provided sufficient control of symptoms. Studies for the use of the subcutaneous dosage form are still limited (Available in KSA).

It is important to note that recommendations from regarding the use of golimumab for the management of systemic JIA were only available on HAS which concluded that there is insufficient data to support the reimbursement for polyarticular JIA.

2.2 Modifications

- A new strength of adalimumab is available on SFDA (80 mg).
- MTX is available as an oral solution on SFDA (2 mg/mL).
- Prednisolone is available as effervescent tablets (2 and 5 mg) as well as in the form of syrup (3 mg/mL) on SFDA.
- The maximum dose of MTX is modified from 20 to 30 MG / M^2 BSA / WEEK.

2.3 Delisting

No medications were delisted from the SFDA.

Section 3.0 Key Recommendations Synthesis

- The use of NSAIDs is conditionally recommended as first-line therapy for oligoarthritis, TMJ arthritis and systemic JIA (Certainty of evidence: very low)[4].
- IAGCs are strongly recommended as initial therapy for the management of oligoarthritis (Certainty of evidence: very low)[4].
- Oral glucocorticoids are conditionally recommended against as first-line therapy for the management of oligoarthritis, TMJ arthritis and systemic JIA without MAS (Certainty of evidence: very low)[4].
- Conventional synthetic DMARDs are strongly advised for cases of insufficient response to or intolerance of NSAIDs and/or IAGCs when managing cases of oligoarthritis and TMJ arthritis[4].
- MTX is conditionally recommended as a preferred agent over LEF, SSZ, and HCQ (in that order) for the treatment of oligoarthritis (Low (MTX); Very low (LEF, SSZ, HCQ))[4].
- In the management of TMJ arthritis, MTX is conditionally recommended as a preferable option over LEF (Certainty of evidence: very low)[4].
- Biologic DMARDs are strongly advised in cases of insufficient response to or intolerance of NSAIDs and/or IAGCs, along with the use of at least one conventional synthetic DMARD in the treatment of oligoarthritis (Certainty of evidence: very low)[4].
- Biologic DMARDs are conditionally recommended in cases of insufficient response to or intolerance of NSAIDs and/or IAGCs, along with the utilization of at least one conventional synthetic DMARD for the management of TMJ arthritis (Certainty of evidence: very low).
- It is conditionally recommended to consider adverse prognostic indicators (such as the engagement of the ankle, wrist, hip, sacroiliac joint, and/or TMJ, the existence of erosive disease or enthesitis, diagnostic delay, heightened inflammation marker levels, and symmetrical disease) as a guide for treatment choices for oligoarthritis and TMJ arthritis (Certainty of evidence: very low)[4].

- Biologic DMARDs (including IL-1 and IL-6 inhibitors) are conditionally suggested for use as initial monotherapy for the management of systemic JIA without MAS. No specific agent is favored (Certainty of evidence: very low)[4].
- IL-1 and IL-6 inhibitors are strongly recommended as a superior choice compared to a single or combined regimen of conventional synthetic DMARDs in cases of insufficient response to or intolerance of NSAIDs and/or glucocorticoids when managing cases of systemic JIA without MAS. (Certainty of evidence: very low)[4].
- For persistent arthritis and incomplete response to IL-1 and/or IL-6 inhibitors, both biologic DMARDs and conventional synthetic DMARDs are highly recommended over extended use of glucocorticoids in the management of systemic JIA without MAS. No specific agent is preferred (Certainty of evidence: very low)[4].
- It is highly advised to have a conversation about a nutrit[4]ious diet suitable for the individual's age (Certainty of evidence: very low).
- The use of a particular diet for addressing JIA is strongly discouraged (Certainty of evidence: very low)[4].
- The use of supplementary or herbal approaches specifically for treating JIA is conditionally discouraged (Certainty of evidence: very low)[4].
- Engaging in physical and occupational therapy is conditionally encouraged regardless of concurrent pharmacologic treatment (Certainty of evidence: very low)[4].
- The suggested approach for treating active uveitis involves using potent topical steroids as the initial treatment. It is advised to start with a concentrated application, followed by a gradual decrease in the amount applied[5].
- For children and adolescents with JIA and CAU who are initiating systemic uveitis treatment, the use of subcutaneous methotrexate is conditionally recommended over oral methotrexate[8].
- For children and adolescents diagnosed with JIA and severe active CAU accompanied by sight-threatening complications, it is conditionally recommended to initiate both MTX and a monoclonal antibody TNFi promptly, in preference to using MTX alone[8].
- For children and adolescents diagnosed with JIA and active CAU who are initiating a TNFi treatment, the initiation of a monoclonal antibody TNFi over etanercept is conditionally recommended[8].

- In cases where children and adolescents with JIA and active CAU exhibit an inadequate response to a monoclonal antibody TNFi at the standard JIA dose, an increase in the dose and/or frequency above the standard level is conditionally recommended instead of switching to a different monoclonal antibody TNFi[8].
- When children and adolescents with JIA and active CAU do not experience success with the first monoclonal antibody TNFi even when administered at an escalated dose and/or frequency, changing to another monoclonal antibody TNFi is conditionally recommended rather than transitioning to a biologic from another category[8].
- In situations where children and adolescents with JIA and active CAU do not achieve desired outcomes after trying methotrexate and two monoclonal antibody TNFi treatments at an above-standard dose and/or frequency, the use of abatacept or tocilizumab as biologic DMARD options, along with mycophenolate, LEF, or cyclosporine as alternative nonbiologic DMARD options, is conditionally recommended[8].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI JIA report** and aims to provide recommendations to aid in the management of JIA. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with JIA. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Juvenile idiopathic arthritis. Accessed August 11, 2023. https://www.mayoclinic.org/diseases-conditions/juvenile-idiopathic-arthritis/symptoms-causes/syc-20374082
2. Al-Mayouf SM, Al Mutairi M, Bouayed K, et al. Epidemiology and demographics of juvenile idiopathic arthritis in Africa and Middle East. *Pediatric Rheumatology*. 2021;19(1). doi:10.1186/s12969-021-00650-x
3. Al-Hemairi MH, Albokhari SM, Muzaffer MA. The Pattern of Juvenile Idiopathic Arthritis in a Single Tertiary Center in Saudi Arabia. *Int J Inflam*. 2016;2016. doi:10.1155/2016/7802957
4. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. *Arthritis Care Res (Hoboken)*. 2022;74(4):521-537. doi:10.1002/acr.24853
5. Sousa CD. *The 2021 Portuguese Society of Ophthalmology Joint Guidelines with Paediatric Rheumatology on the Screening, Monitoring and Medical Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis*. Vol 10. www.arprheumatology.com
6. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):703-716. doi:10.1002/acr.23871
7. Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging. *Arthritis Care Res (Hoboken)*. 2022;74(4):505-520. doi:10.1002/acr.24839
8. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of Juvenile Idiopathic Arthritis–Associated Uveitis. *Arthritis Care Res (Hoboken)*. 2019;71(6):703-716. doi:10.1002/acr.23871
9. Angeles-Han ST, Lo MS, Henderson LA, et al. Childhood arthritis and rheumatology research alliance consensus treatment plans for juvenile idiopathic arthritis–Associated and idiopathic chronic anterior uveitis. *Arthritis Care Res (Hoboken)*. 2019;71(4):482-491. doi:10.1002/acr.23610
10. Lexicomp. Published 2023. Accessed June 6, 2023. https://online-lexi-com.ezproxy.lau.edu.lb:2443/lco/action/home

11. Quartier P, Allantaz F, Cimaz R, et al. A multicenter, randomized, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis*. 2011;70(5):747-754. doi:10.1136/ard.2010.134254

12. *Anakinra for Treating Still's Disease*.; 2021. www.nice.org.uk/guidance/ta685

13. anakinra. Accessed August 14, 2023. https://www.cadth.ca/anakinra

14. kineret_summary_ct17195.

15. anakinra. Accessed August 14, 2023. https://www.pbs.gov.au/medicine/item/10263E-10264F

16. Ruperto N, Brunner HI, Synoverska O, et al. Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomized trial. *The Lancet*. 2021;398(10315):1984-1996. doi:10.1016/S0140-6736(21)01255-1

17. *Tofacitinib for Treating Juvenile Idiopathic Arthritis*.; 2021. www.nice.org.uk/guidance/ta735

18. XELJANZ (tofacitinib) - Juvenile arthritis. Accessed August 16, 2023. https://www.has-sante.fr/jcms/p_3337944/en/xeljanz-tofacitinib-arthrite-juvenile

19. for Quality I, in Health Care E. *A21-121 - Tofacitinib - Extract of Dossier Assessment - Version 1.0*. www.iqwig.de

20. Lexicomp 2023.

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Juvenile Idiopathic Arthritis Scope

2020	Changes	2023	Rationale
Section 1.0 JIA Clinical Guidelines			
2019 ACR/Arthritis Foundation Guideline for the Treatment of JIA: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis .	N/A		
NICE guidelines for Abatacept, ADA, etanercept and Abatacept, ADA, etanercept and tocilizumab for treating JIA 2015	N/A		
Management of JIA 2015: A Position Statement from the Pediatric Committee of the Canadian Rheumatology Association	N/A		
2013 Update of the 2011 ACR Recommendations for the Treatment of JIA: Recommendations for the Medical Therapy of Children	N/A		

with Systemic JIA and Tuberculosis Screening Among Children Receiving Biologic Medications			
	Missing	2021 ACR Guideline for the Treatment of JIA: Therapeutic Approaches for Oligoarthritis, TMJ Arthritis, and Systemic JIA[4]	**Oligoarticular JIA** Oligoarthritis refers to JIA presenting with involvement of ≤4 joints without systemic manifestations**.** • It is **strongly** recommended to use schedule NSAIDs as part of initial therapy (Certainty of evidence: very low). • IAGCs are **strongly** recommended as part of initial therapy (Certainty of evidence: very low). • Triamcinolone hexacetonide is **strongly** recommended as the preferred agent (Certainty of evidence: low). • Oral glucocorticoids are **conditionally** recommended against as part of initial therapy (Certainty of evidence: very low). • Conventional synthetic DMARDs are **strongly** recommended if there is an inadequate response to scheduled NSAIDs and/or IAGCs. MTX is conditionally recommended as a preferred agent over LEF, Sulfasalazine (SSZ), and Hydroxychloroquine (HCQ) (Certainty of evidence: Low (MTX); Very low (LEF, SSZ, HCQ)) Biologic DMARDs are **strongly**

			recommended if there is inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 conventional synthetic DMARD. There is no preferred biologic DMARD (Certainty of evidence: very low). • Considering risk factors for a poor outcome (such as the involvement of the ankle, wrist, hip, sacroiliac joint, and/or TMJ, the presence of erosive disease or enthesitis, a delay in diagnosis, elevated levels of inflammation markers, and symmetric disease) is **conditionally** recommended to guide decisions regarding treatment (Certainty of evidence: very low). • The use of validated measures for assessing disease activity is **conditionally** recommended to aid in making treatment decisions, particularly to support the implementation of treat-to-target strategies (Certainty of evidence: very low). **Temporomandibular joint arthritis** • TMJ disorder could exist independently or be a component of widespread arthritis. Managing TMJ arthritis is crucial, given that patients and caregivers have highlighted its significant effects on the quality of oral health-related life and difficulties in diagnosing and achieving effective pharmacological remedies.

			• A trial of scheduled NSAIDs is **conditionally** recommended as part of initial therapy (Certainty of evidence: very low). • IAGCs are **conditionally** recommended as part of initial therapy (Certainty of evidence: very low). There is no preferred agent (Certainty of evidence: very low). • Oral glucocorticoids are **conditionally** recommended against as part of initial therapy (Certainty of evidence: very low). • Conventional synthetic DMARDs are strongly **recommended** for inadequate response to or intolerance of NSAIDs and/or IAGCs. MTX is conditionally recommended as a preferred agent over LEF (Certainty of evidence: very low). • Biologic DMARDs are **conditionally** recommended for inadequate response to or intolerance of NSAIDs and/or IAGCs and at least 1 conventional synthetic DMARD. There is no preferred biologic agent (Certainty of evidence: very low). • The evaluation of unfavorable predictive characteristics (such as the engagement of the ankle, wrist, hip, sacroiliac joint, and/or TMJ, existence of erosive disease or enthesitis, delayed diagnosis, elevated inflammation marker levels, and symmetrical disease) is **conditionally** recommended for informing decisions related to treatment (Certainty of evidence: very low).

			Systemic JIA • Systemic JIA stands apart from other forms of JIA due to the presence of fever, rash, and internal organ participation. Some experts view it as an autoinflammatory disorder. **Systemic JIA without MAS** • NSAIDs are conditionally recommended as initial monotherapy. Oral glucocorticoids are **conditionally** recommended against as initial monotherapy (Certainty of evidence: very low). • Conventional synthetic DMARDs are **strongly** recommended against as initial monotherapy (Certainty of evidence: very low). • Biologic DMARDs (Interleukin-1 (IL-1) and Interleukin-6 (IL-6) inhibitors) are **conditionally** recommended as initial monotherapy. There is no preferred agent (Certainty of evidence: very low). • IL-1 and IL-6 inhibitors are **strongly** recommended over a single or combination of conventional synthetic DMARDs for inadequate response to or intolerance of NSAIDs and/or glucocorticoids (Certainty of evidence: very low). • Biologic DMARDs or conventional synthetic DMARDs are **strongly** recommended over long-term

			glucocorticoids for residual arthritis and incomplete response to IL-1 and/ or IL-6 inhibitors. There is no preferred agent (Certainty of evidence: very low). **Systemic JIA with MAS** • IL-1 and IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS. Glucocorticoids are **conditionally** recommended as part of initial treatment of systemic JIA with MAS. There is no preferred agent (Certainty of evidence: very low). • Biologic DMARDs or conventional synthetic DMARDs are **strongly** recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors. There is no preferred agent (Certainty of evidence: very low). **Systemic JIA with inactive disease** • Tapering down and discontinuing the use of glucocorticoids is **strongly** advised once a state of inactive disease has been achieved (Certainty of evidence: very low). • Tapering and discontinuing biologic DMARDs is **conditionally** recommended after inactive disease has been reached (Certainty of evidence: very low).

	Missing	2021 ACR Guideline for the Treatment of JIA: Recommendations for Nonpharmacologic Therapies, Medication Monitoring, Immunizations, and Imaging[7]	**Nonpharmacologic therapies** • A discussion of a healthy, age-appropriate diet is strongly recommended (Certainty of evidence: very low). • Use of a specific diet to treat JIA is strongly recommended against (Certainty of evidence: very low). • Use of supplemental or herbal interventions specifically to treat JIA is conditionally recommended against (Certainty of evidence: very low). • Physical and occupational therapy are conditionally recommended regardless of concomitant pharmacologic therapy (Certainty of evidence: very low). Medication monitoring • NSAIDs: Monitoring via CBC counts, LFTs, and renal function tests every 6–12 months is **conditionally** recommended (Certainty of evidence: very low). • MTX: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **strongly** recommended (Certainty of evidence: very low).

			• Decreasing the MTX dosage or withholding MTX is **conditionally** recommended in the presence of a clinically significant increase in LFTs readings or a decrease in neutrophil or platelet counts (Certainty of evidence: very low). • Use of folic/folinic acid in conjunction with MTX is **strongly** recommended (Certainty of evidence: very low). • SSZ: Monitoring via CBC counts, LFTs, and renal function tests within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended (Certainty of evidence: very low). • Decreasing the SSZ dosage or withholding SSZ is **conditionally** recommended if a clinically relevant elevation in LFTs results or decreased neutrophil or platelet count is detected (Certainty of evidence: very low) • LEF: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3-4 months thereafter is **conditionally** recommended (Certainty of evidence: very low) • Altering LEF administration is **conditionally** recommended if a clinically relevant elevation in LFTs results occurs (temporary withholding of LEF if the ALT level is >3 times the upper limit of normal [ULN]), as per the package

			insert (Certainty of evidence: very low). • Baseline and annual retinal screening after starting HCQ are **conditionally** recommended (Certainty of evidence: very low). • HCQ: Monitoring via CBC counts and LFTs annually is **conditionally** recommended (Certainty of evidence: very low). • TNFi: Monitoring via CBC counts and LFTs annually is **conditionally** recommended (Certainty of evidence: very low). • Abatacept: Doing no routine laboratory monitoring is **conditionally** recommended (Certainty of evidence: very low). • Tocilizumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels every 6 months is conditionally recommended, as per the package insert (Certainty of evidence: very low). • Anakinra: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended (Certainty of evidence: very low). • Canakinumab: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended (Certainty of evidence: very low).

			• Tofacitinib: Monitoring via CBC counts and LFTs within the first 1–2 months of usage and every 3–4 months thereafter is **conditionally** recommended. Monitoring of lipid levels 1–2 months after starting treatment is **conditionally** recommended, as per the package insert. Altering tofacitinib administration is strongly recommended if monitoring reveals laboratory abnormalities of concern. Specifically, medication should be discontinued if the hemoglobin level is 2 gm/dl, or for severe neutropenia (<500/mm3) or lymphopenia (<500/ mm3), as per the package insert (Given recent approval for JIA and limited experience, recommendations are based on clinical trial, US Food and Drug Administration guidance, and evidence in adult) **Infection surveillance/immunizations** • No consensus achieved regarding the need to obtain infection titers (measles, varicella, hepatitis B, hepatitis C) for all children with JIA checked prior to starting immunosuppressive medication (Certainty of evidence: very low). • Immunization is **conditionally** recommended for children with active non-systemic JIA who have not yet been immunized for measles, mumps, rubella, and/or varicella prior to starting

			immunosuppressive medications (Certainty of evidence: very low). • Tuberculosis (TB) screening is **conditionally** recommended prior to starting biologic DMARD therapy and when there is a concern for TB exposure thereafter (Certainty of evidence: very low). • Immunizations (live and inactivated) are **strongly** recommended for children with JIA who are not receiving immunosuppressive treatment (Certainty of evidence: very low). • Annual inactivated influenza immunization is **strongly** recommended for all children with JIA (Certainty of evidence: very low). • Inactivated vaccines are **strongly** recommended for children who are receiving immunosuppressive treatment (Certainty of evidence: very low). • Live attenuated vaccines are **conditionally** recommended against in children with JIA who are receiving immunosuppressive treatment (Certainty of evidence: low). • Vaccines are **strongly** recommended for household contacts of children with JIA who are receiving immunosuppressive treatment (Certainty of evidence: very low). **Imaging** • Use of radiography as a screening test prior to

			advanced imaging, for the purpose of identifying active synovitis or enthesitis, is **strongly** recommended against (Certainty of evidence: very low). • Imaging guidance is **conditionally** recommended for use with IAGCs injections of joints that are difficult to access, or to specifically localize the distribution of inflammation (Certainty of evidence: very low).
	Missing	2019 ACR/Arthritis Foundation Guideline for the Screening, Monitoring, and Treatment of JIA-U	• In children and adolescents with JIA at high risk of developing uveitis, ophthalmic screening every 3 months is **conditionally** recommended over screening at a different frequency. • In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing topical glucocorticoids, ophthalmic monitoring within 1 month after each change of topical glucocorticoids is **strongly** recommended over monitoring less frequently.

			• In children and adolescents with JIA and controlled uveitis on stable therapy, ophthalmic monitoring no less frequently than every 3 months is **strongly** recommended over monitoring less frequently. • In children and adolescents with JIA and controlled uveitis who are tapering or discontinuing systemic therapy, ophthalmic monitoring within 2 months of changing systemic therapy is **strongly** recommended over monitoring less frequently. • In children and adolescents with JIA and active chronic anterior uveitis (CAU), using prednisolone acetate 1% topical drops is **conditionally** recommended over difluprednate topical drops. • In children and adolescents with JIA and active CAU, adding or increasing topical glucocorticoids for short-term control is **conditionally**

			recommended over adding systemic glucocorticoids. • In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for uveitis control, and not on systemic therapy, adding systemic therapy in order to taper topical glucocorticoids is **conditionally** recommended over not adding systemic therapy and maintaining on topical glucocorticoids only. • In children and adolescents with JIA who develop new CAU activity despite stable systemic therapy, topical glucocorticoids prior to changing/escalating systemic therapy are **conditionally** recommended over changing/escalating systemic therapy immediately. • In children and adolescents with JIA and CAU still requiring 1–2 drops/day of prednisolone acetate 1% (or equivalent) for at

			least 3 months and on systemic therapy for uveitis control, changing or escalating systemic therapy is **conditionally** recommended over maintaining current systemic therapy. • In children and adolescents with JIA and CAU who are starting systemic treatment for uveitis, using subcutaneous MTX is **conditionally** recommended over oral methotrexate. • In children and adolescents with JIA with severe active CAU and sight-threating complications, starting MTX and a monoclonal antibody TNFi immediately is **conditionally** recommended over MTX as monotherapy. • In children and adolescents with JIA and active CAU starting a TNFi, starting a monoclonal antibody TNFi is **conditionally** recommended over etanercept. • In children and adolescents with JIA and active CAU who have an inadequate

			response to 1 monoclonal antibody TNFi at standard JIA dose, escalating the dose and/ or frequency to above standard is **conditionally** recommended over switching to another monoclonal antibody TNFi. • In children and adolescents with JIA and active CAU who have failed a first monoclonal antibody TNFi at above-standard dose and/or frequency, changing to another monoclonal antibody TNFi is **conditionally** recommended over a biologic in another category. • In children and adolescents with JIA and active CAU who have failed methotrexate and 2 monoclonal antibody TNFi at above-standard dose and/or frequency, the use of abatacept or tocilizumab as biologic DMARD options, and mycophenolate, LEF, or cyclosporine as alternative nonbiologic DMARD options is **conditionally** recommended.

			• In children and adolescents with spondyloarthritis, **strongly** recommend education regarding the warning signs of acute anterior uveitis (AAU) for the purpose of decreasing delay in treatment, duration of symptoms, or complications of iritis. • In children and adolescents with spondyloarthritis otherwise well **controlled** with systemic immunosuppressive. therapy (DMARDs, biologics) who develop AAU, **conditionally** recommend against switching systemic immunosuppressive.
	Missing	CARRA consensus treatment plans for juvenile idiopathic arthritis-associated and idiopathic chronic anterior uveitis (2019)[9]	• CARRA formulated consensus treatment plans (CTPs) for CAU with the aim of minimizing differences in practice approaches and enabling future assessments of treatments through comparative effectiveness analysis methods. • The initial CTP is designed for children who have not yet been exposed to steroid-sparing medications, while the second one is intended for children beginning biologic therapy, offering choices including MTX, adalimumab, and infliximab.

			• Patients with CAU who have not been treated with steroid-sparing therapy can benefit from the MTX CTP. While many experts favor subcutaneous MTX due to its higher bioavailability, there is insufficient evidence to confirm its superior efficacy. Surveys of pediatric rheumatologists reveal that both oral and subcutaneous routes are utilized equally. Hence, both methods are viable options for MTX treatment. The recommended MTX dosage is 0.5-1 mg/kg per week, capped at a maximum of 30 mg weekly, with a preference for doses closer to 1 mg/kg/week. • Patients who do not respond to MTX treatment should be evaluated for the TNFi CTP using monoclonal antibody TNFi. If patients can tolerate MTX, TNFi should be added alongside MTX rather than replacing it. The TNFi CTP may also be an option for MTX-naïve patients with uncontrolled uveitis and severe disease, such as structural complications from uveitis or complications from topical steroid therapy. Simultaneously, MTX treatment, either oral or subcutaneous, from the MTX CTP should be initiated. • There was unanimous agreement that etanercept has no role in the treatment of pediatric uveitis, and that there is insufficient data to recommend either ADA or infliximab as the preferred agent.

			• The TNFi CTP includes three treatment options: 1) ADA SQ injections weekly, 2) ADA SQ injections every other week, and 3) infliximab infusions every 4 weeks after loading. • **MTX intolerance:** The management recommendations for addressing MTX intolerance were deemed outside the scope of these CTPs. The workgroup highlights those methods such as anti-emetics, folic acid, and/or leucovorin use, along with dosage adjustments, can often effectively address MTX intolerance. However, children facing MTX intolerance could also be candidates for the TNFi CTP. • Systemic Steroids: The workgroup recognized that decisions regarding the administration and dosage of systemic and topical corticosteroids are generally determined by ophthalmologists rather than rheumatologists. Consequently, this CTP does not provide corticosteroid guidance. Nevertheless, expert consensus suggests avoiding systemic steroids for treating CAU. Systemic steroids should only serve as a temporary solution while awaiting the effectiveness of steroid-sparing treatment, and their tapering should commence within two weeks of initiating a steroid-sparing agent. • There are insufficient data to recommend treatment of

			uveitis refractory to MTX and TNFi.
	Missing	The 2021 Portuguese Society of Ophthalmology joint guidelines with Paediatric Rheumatology on the screening, monitoring and medical treatment of JIA-U[5]	**Screening, monitoring and medical treatment of JIA-U** • The ongoing monitoring and care of these patients need to be approached in a collaborative manner, involving a multidisciplinary team. An effective partnership between a skilled ophthalmologist and a pediatric rheumatologist is essential, with shared duties and a close working relationship. • A complete set of clinical data should be documented in the patient's record. • Pediatric patients who have idiopathic chronic anterior uveitis and test positive for ANA but do not have a confirmed diagnosis of JIA should receive similar management as those with uveitis associated with JIA. • Screening for uveitis should be initiated in all children as soon as there is suspicion or investigation of JIA, rather than delaying until the disease is definitively confirmed. • When conducting ophthalmological screening for JIA patients, the slit lamp examination is obligatory. • The screening schedule for these children should be adjusted based on their likelihood of developing uveitis. • Regular screening is necessary for both children

			with ongoing uveitis activity and those with inactive uveitis who are undergoing a reduction in immunosuppressive treatment. • Children with active uveitis and children with inactive uveitis in whom immunosuppressive treatment is being de-escalated should be screened regularly. • Initiation of treatment for anterior uveitis should commence when there are ≥0.5 AC cells. • For active uveitis, primary treatment with high-potency topical steroids is recommended. These should be administered initially in a concentrated burst, followed by a gradual reduction in dosage. • When there is evident inflammatory activity (0.5 cells or higher in the anterior chamber), cycloplegics should be included in the treatment regimen. • In cases of complex disease or when sight-threatening complications are present, systemic steroids should be contemplated to swiftly manage inflammation. • Extended administration of systemic steroids should be minimized to prevent potential adverse outcomes. • For children who do not adequately respond to topical steroids or exhibit substantial structural complications, the commencement of immunosuppressive

			treatment should not be postponed. • In patients who do not respond well to topical steroids or who have notable structural complications, MTX should be employed as the initial treatment option. Additionally, consistent monitoring for potential adverse effects should be conducted. • In the case of Juvenile JIA-U, the preferred initial biologic medication is ADA. • When advancing to ADA treatment, it is advisable to continue with MTX unless there are contraindications or adverse reactions. • Continuous monitoring of long-term MTX and ADA treatment should be carried out by a pediatric rheumatologist. • Etanercept is contraindicated for children with JIA-U and should be steered clear of when addressing joint symptoms of JIA in individuals with a uveitis history. • If there are indications of inadequate response to ADA (such as insufficient inflammation control or repeated use of topical steroids for recurring/persistent uveitis), it is advisable to assess ADA serum levels, ascertain the presence of neutralizing antibodies, and reevaluate the treatment approach. • If the joint use of MTX and ADA fails to effectively manage ocular inflammation, the option of transitioning treatment to infliximab,

			tocilizumab, abatacept, or rituximab should be considered. • The possibility of reducing or discontinuing immunosuppressants may be contemplated following a period of 2 years without uveitis activity. • The use of periocular or intravitreal steroids should only be contemplated for JIA-U instances that do not respond to optimized systemic treatment or involve severe complications jeopardizing vision. • In cases where ocular surgery is required, such as for cataract or glaucoma, the administration of perioperative supplementary treatment (which may involve systemic and topical steroids) should be meticulously coordinated between the ophthalmologist and pediatric rheumatologist. • Families and, if of appropriate age, patients themselves should receive comprehensive information regarding the potential occurrence of uveitis in JIA. • Active involvement of both the patient and their family in collaborative care, including discussions about follow-up, treatment approaches, and prognosis, is of utmost importance. • Additional conventional immunosuppressive medications (like mycophenolate mofetil, azathioprine, or cyclosporine) could be considered if there are contraindications,

			intolerance, or toxicity associated with MTX. However, there isn't sufficient evidence to firmly establish any of these drugs as definitive second-line treatments for rescuing patient's refractory to MTX.

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for JIA

The following is the result of the PubMed search conducted for diabetic retinopathy guideline search:

Query	Filters	Search Details	Results
((Arthritis, Juvenile[MeSH Terms])) OR (Juvenile Arthritis[Title/Abstract])) OR (Childhood Arthritis[Title/Abstract])) OR (Arthritides, Childhood[Title/Abstract])) OR (Arthritis, Childhood[Title/Abstract])) OR (Childhood Arthritides[Title/Abstract])) OR (Arthritis, Juvenile Chronic[Title/Abstract])) OR (Juvenile Chronic Arthritis[Title/Abstract])) OR (Chronic Arthritis, Juvenile[Title/Abstract])) OR (Juvenile Idiopathic Arthritis[Title/Abstract])) OR (Idiopathic Arthritis, Juvenile[Title/Abstract])) OR (Arthritis, Juvenile Idiopathic[Title/Abstract])) OR (Juvenile Rheumatoid Arthritis[Title/Abstract])) OR (Arthritis, Juvenile	Guideline, in the last 5 years	("arthritis, juvenile"[MeSH Terms] OR "juvenile arthritis"[Title/Abstract] OR "childhood arthritis"[Title/Abstract] OR (("Arthritis"[MeSH Terms] OR "Arthritis"[All Fields] OR "Arthritides"[All Fields] OR "polyarthritides"[All Fields]) AND "Childhood"[Title/Abstract]) OR "arthritis childhood"[Title/Abstract] OR "childhood arthritides"[Title/Abstract] OR "arthritis juvenile chronic"[Title/Abstract] OR "juvenile chronic arthritis"[Title/Abstract] OR "chronic arthritis juvenile"[Title/Abstract] OR "juvenile idiopathic arthritis"[Title/Abstract] OR "idiopathic arthritis juvenile"[Title/Abstract] OR "arthritis juvenile idiopathic"[Title/Abstract] OR "juvenile rheumatoid arthritis"[Title/Abstract] OR "arthritis juvenile rheumatoid"[Title/Abstrac	9

Rheumatoid[Title/Abstract])) OR (Rheumatoid Arthritis, Juvenile[Title/Abstract])) OR (Oligoarthritis, Juvenile[Title/Abstract])) OR (Juvenile Oligoarthritis[Title/Abstract])) OR (Psoriatic Arthritis, Juvenile[Title/Abstract])) OR (Arthritis, Juvenile Psoriatic[Title/Abstract])) OR (Juvenile Psoriatic Arthritis[Title/Abstract])) OR (Enthesitis-Related Arthritis, Juvenile[Title/Abstract])) OR (Arthritis, Juvenile Enthesitis-Related[Title/Abstract])) OR (Enthesitis Related Arthritis, Juvenile[Title/Abstract])) OR (Juvenile Enthesitis-Related Arthritis[Title/Abstract])) OR (Polyarthritis, Juvenile, Rheumatoid Factor Negative[Title/Abstract])) OR (Juvenile-Onset Still Disease[Title/Abstract])) OR (Juvenile Onset Still Disease[Title/Abstract])) OR (Still Disease, Juvenile-Onset[Title/Abstract])) OR (Still Disease, Juvenile Onset[Title/Abstract])) OR (Still's Disease, Juvenile-Onset[Title/Abstract])) OR (Juvenile-Onset Still's		t] OR "rheumatoid arthritis juvenile"[Title/Abstract] OR "oligoarthritis juvenile"[Title/Abstract] OR "juvenile oligoarthritis"[Title/Abstract] OR "psoriatic arthritis juvenile"[Title/Abstract] OR "arthritis juvenile psoriatic"[Title/Abstract] OR "juvenile psoriatic arthritis"[Title/Abstract] OR "enthesitis related arthritis juvenile"[Title/Abstract] OR (("Arthritis"[MeSH Terms] OR "Arthritis"[All Fields] OR "Arthritides"[All Fields] OR "polyarthritides"[All Fields]) AND "juvenile enthesitis related"[Title/Abstract]) OR "enthesitis related arthritis juvenile"[Title/Abstract] OR "juvenile enthesitis related arthritis"[Title/Abstract] OR (("arthritis, juvenile"[MeSH Terms] OR ("Arthritis"[All Fields] AND "Juvenile"[All Fields]) OR "juvenile arthritis"[All Fields] OR ("polyarthritis"[All Fields] AND "Juvenile"[All Fields]) OR "polyarthritis juvenile"[All Fields]) AND "rheumatoid factor negative"[Title/Abstract]) OR ("Juvenile-Onset"[All Fields] AND "still disease"[Title/Abstract]) OR (("Juvenile"[All Fields] OR "juvenile s"[All Fields] OR "juveniles"[All Fields]	

Disease[Title/Abstract])) OR (Still's Disease, Juvenile Onset[Title/Abstract])) OR (Systemic Arthritis, Juvenile[Title/Abstract])) OR (Arthritis, Juvenile Systemic[Title/Abstract])) OR (Juvenile Systemic Arthritis[Title/Abstract])) OR (Juvenile-Onset Stills Disease[Title/Abstract])) OR (Juvenile Onset Stills Disease[Title/Abstract])) OR (Stills Disease, Juvenile-Onset[Title/Abstract])) OR (Polyarthritis, Juvenile, Rheumatoid Factor Positive[Title/Abstract])) OR (Polyarticular Juvenile Idiopathic Arthritis[Title/Abstract])) OR (Polyarticular-Course Juvenile Idiopathic Arthritis[Title/Abstract])) OR (PCJIA[Title/Abstract])) OR (PJIA Polyarticular Juvenile Idiopathic Arthritis[Title/Abstract])		OR "juvenility"[All Fields]) AND "onset still disease"[Title/Abstract]) OR (("arthritis, juvenile"[MeSH Terms] OR ("Arthritis"[All Fields] AND "Juvenile"[All Fields]) OR "juvenile arthritis"[All Fields] OR ("Still"[All Fields] AND "Disease"[All Fields]) OR "still disease"[All Fields]) AND "Juvenile-Onset"[Title/Abstract]) OR (("arthritis, juvenile"[MeSH Terms] OR ("Arthritis"[All Fields] AND "Juvenile"[All Fields]) OR "juvenile arthritis"[All Fields] OR ("Still"[All Fields] AND "Disease"[All Fields]) OR "still disease"[All Fields]) AND "Juvenile-Onset"[Title/Abstract]) OR (("arthritis, juvenile"[MeSH Terms] OR ("Arthritis"[All Fields] AND "Juvenile"[All Fields]) OR "juvenile arthritis"[All Fields] OR ("Still's"[All Fields] AND "Disease"[All Fields]) OR "still s disease"[All Fields]) AND "Juvenile-Onset"[Title/Abstract]) OR "juvenile onset still s disease"[Title/Abstract] OR (("arthritis, juvenile"[MeSH Terms] OR ("Arthritis"[All Fields] AND "Juvenile"[All Fields]) OR "juvenile arthritis"[All Fields] OR ("Still's"[All Fields] AND "Disease"[All Fields]) OR "still s disease"[All Fields]) AND "Juvenile-Onset"[Title/Abstract]) OR (("Systemic"[All Fields] OR "systemically"[All Fields]	

		OR "systemics"[All Fields]) AND "arthritis juvenile"[Title/Abstract]) OR "arthritis juvenile systemic"[Title/Abstract] OR "juvenile systemic arthritis"[Title/Abstract] OR ("Juvenile-Onset"[All Fields] AND "stills disease"[Title/Abstract]) OR (("Juvenile"[All Fields] OR "juvenile s"[All Fields] OR "juveniles"[All Fields] OR "juvenility"[All Fields]) AND "onset stills disease"[Title/Abstract]) OR (("Stills"[All Fields] AND ("Disease"[MeSH Terms] OR "Disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields])) AND "Juvenile-Onset"[Title/Abstract]) OR (("arthritis, juvenile"[MeSH Terms] OR ("Arthritis"[All Fields] AND "Juvenile"[All Fields]) OR "juvenile arthritis"[All Fields] OR ("polyarthritis"[All Fields] AND "Juvenile"[All Fields]) OR "polyarthritis juvenile"[All Fields]) AND "rheumatoid factor positive"[Title/Abstract]) OR "polyarticular juvenile idiopathic arthritis"[Title/Abstract] OR "polyarticular course juvenile idiopathic arthritis"[Title/Abstract] OR "PCJIA"[Title/Abstract] OR ("PJIA"[All Fields] AND "polyarticular juvenile idiopathic arthritis"[Title/Abstract]))	

Appendix D. Treatment Algorithm

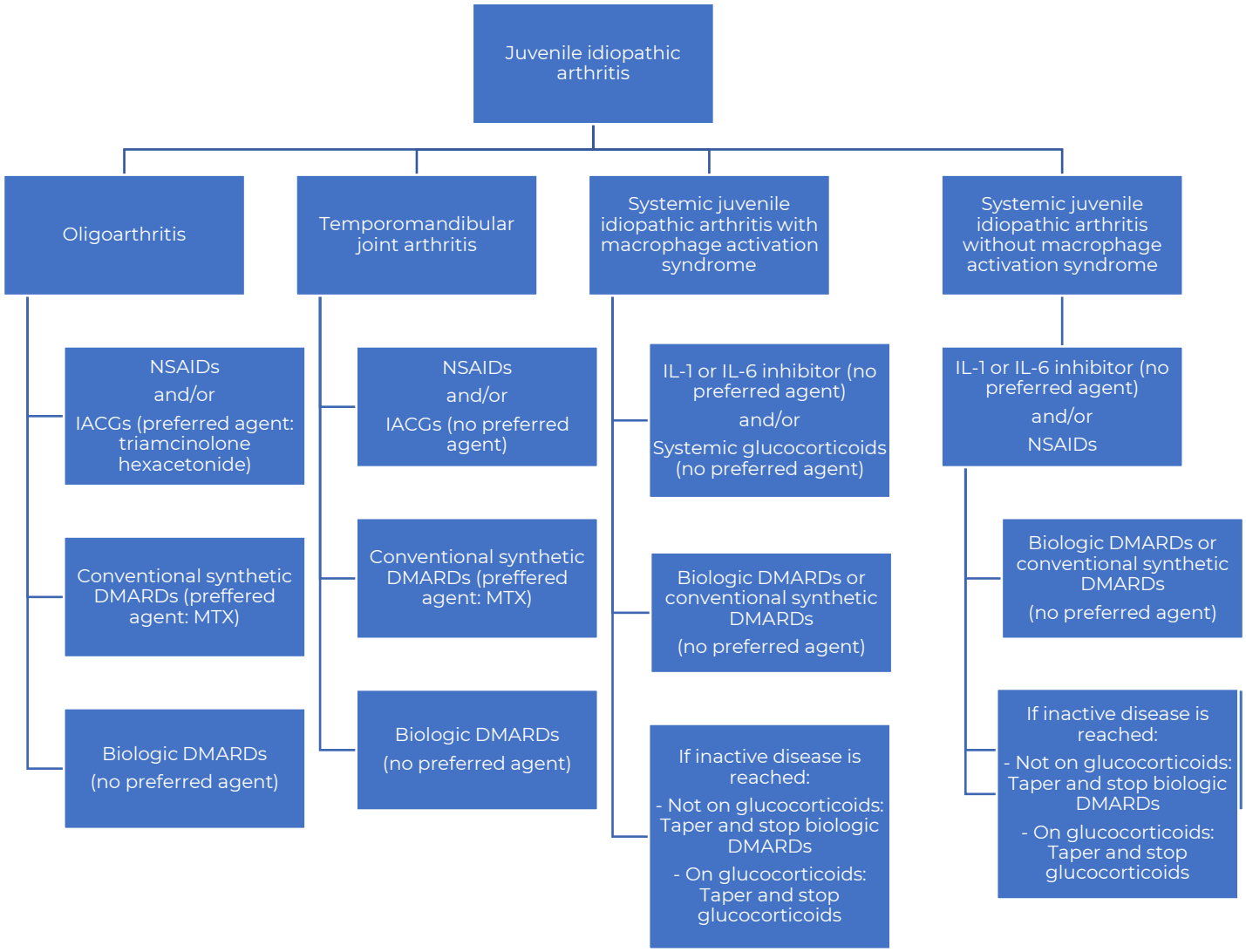


Figure 4. *Treatment Algorithm for the Management of Juvenile Idiopathic Arthritis*