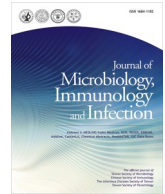




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Taiwan guideline for the diagnosis and management of juvenile idiopathic arthritis: Consensus statement of the Taiwan Academy of Pediatric Allergy, Asthma and Immunology

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is one of the most common types of arthritis to affect children, with onset occurring under the age of 16. Primarily characterized by chronic inflammation of the synovium, JIA is actually a heterogeneous disease, comprising several subtypes. It is therefore important to accurately identify the disease subtype, and subsequently prescribe treatments that can target the corresponding disease mechanisms. Regular monitoring during and after treatment is also necessary to mitigate related risks and adverse effects. In Taiwan, epidemiological research has shown that enthesitis-related arthritis (ERA) is the predominant JIA subtype (38.6% of all cases), which differs from the epidemiological features in other countries. The Taiwan Academy of Pediatric Allergy, Asthma and Immunology (TAPAAI) therefore developed this guideline with these epidemiological characteristics in mind, and further draws upon the latest clinical evidence regarding JIA diagnosis, monitoring, and newly approved treatments, as well as recently published JIA guidelines from the United States and Germany. It is hoped that this guideline can serve as a practical and up-to-date reference for healthcare professionals, and support daily clinical practice for the enhancement of patient outcomes.

1. Introduction

Juvenile idiopathic arthritis (JIA) is one of the most common chronic joint diseases in children under the age of 16, and imposes a considerable health, economic, and social burden on patients and their families. The emergence of biologics and the recent approval of Janus kinase inhibitors (JAKi) has provided clinicians with an expanded range of treatment options, but the heterogeneous etiology of JIA means that diagnosis, treatment, and monitoring remain highly complex, and thereby require the support of up-to-date evidence and clinically relevant management guidelines. The Taiwan Academy of Pediatric Allergy,

Asthma and Immunology (TAPAAI) therefore sought to develop a guideline for the diagnosis and management of JIA, taking into consideration the epidemiological characteristics of the local patient population and the latest clinical evidence available. A working group of 6 pediatric rheumatology experts was established to draft the guideline, and the TAPAAI committee of 23 experts reviewed the completed draft. The latest relevant research on JIA, recent guidelines published by the American College of Rheumatology (ACR) and the German Society for Pediatric Rheumatology (GKJR), and expert opinions derived from experienced pediatric rheumatology specialists in Taiwan were incorporated into this guideline. Five guideline working group meetings were

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held from July 2023 to July 2024. Consensus recommendations were discussed and approved at the TAPAAI committee meeting on June 16, 2024. The final guideline provides a comprehensive overview of JIA epidemiology, clinical characteristics, pathogenesis, diagnosis, treatment, prognosis, and monitoring. A Chinese version of the guideline has also been made available on the TAPAAI official website (<http://www.air.org.tw>). It is hoped that this guideline can serve as a practical reference for healthcare professionals, and help to support and enhance clinical practice for the betterment of patient outcomes. Regular updates to the guideline are being planned to ensure access to the latest clinical evidence for JIA.

2. Epidemiology and clinical characteristics

Consensus statements on JIA characteristics are presented in Table 1. Epidemiological studies of JIA in Taiwan are primarily based on the National Health Insurance Research Database (NHIRD),^{1–3} which comprises 99.99% of the local population.⁴ Studies spanning the NHIRD from 1999 to 2009 revealed JIA incidence rates of 4.93–15.7/100,000 persons (6.0–16.8/100,000 persons in boys and 3.8–14.5/100,000 persons in girls), with incidence found to be higher in the 10–15 age group compared to the 6–9 and 0–4 age group.^{2,3} JIA prevalence rates were reported to be 29.7–33.8/100,000 persons (32.1–40.7/100,000 persons in boys and 26.3–27.1/100,000 persons in girls),^{2,3} with the male to female ratio of patients being 1.69 to 1.^{2,5} Overall, the incidence and prevalence of JIA in Taiwan are higher than reported in Japan,^{6,7} but lower than reported in the United States and Europe.^{8–12} The primary JIA subtype in Taiwan is enthesitis-related arthritis (ERA), which accounts for 38.6% of all cases (Fig. 1)^{5,13}; this may be a factor behind the older age at disease onset seen in Taiwan (mean age of onset: 11.5 ± 3.7 years)^{2,3,5} as compared to other countries (Table 2).^{6–15}

JIA is a highly heterogeneous disease with several subtypes, each with differing mechanisms and prognosis. The widely adopted International League of Associations for Rheumatology (ILAR) classification criteria for JIA stratifies patients into seven mutually exclusive subtypes, based on the number of affected joints, family history, extra-articular manifestations, rheumatoid factor (RF) positivity, and human leukocyte antigen (HLA)-B27 positivity.^{16,17} However, the ILAR criteria has several limitations; for example, some subtypes are not well-characterized,¹⁸ and the exclusion criteria regarding HLA-B27 positivity or family history of psoriasis¹⁹ can cause a substantial cohort of patients to become unclassifiable.^{18,20} Moreover, subtypes are not strongly correlated with disease pathogenesis.^{18,20} In light of this, the Pediatric Rheumatology International Trials Organization (PRINTO) has proposed a new definition of JIA that comprises six subtypes²¹; however, further large-scale studies will be needed to validate the PRINTO criteria.²²

3. Pathogenesis

Both genetic and environmental factors are involved in the development of JIA.^{23–28,35} The complexity of JIA pathogenesis in different subtypes is shown in Fig. 2.^{30–34,37} Systemic JIA has been seen as part of the autoinflammatory disease spectrum. Based on the observation of biphasic disease progression and evolution over time, systemic JIA is initially driven by innate immune activation and dysregulation, with major roles for IL-1 β and marked elevation of IL-6, IL-18, and S100 proteins.³³ However, as systemic JIA progresses, uncontrolled innate inflammatory mediators can drive the activation of adaptive immune cells, especially T cells.^{33,38}

Oligoarticular and polyarticular JIA are characterized by loss of immune tolerance and joint-specific and systemic autoimmunity driven by adaptive immunity, with activation of pro-inflammatory Th1/Th17 CD4⁺ T cells, CD8⁺ T cells, synovial- or enthesal-resident memory T cells, and dysfunctional regulatory T cells.^{29,33,39} B cells and autoantibodies such as RF, anti-cyclic citrullinated peptide (anti-CCP) antibodies, and anti-nuclear antibody (ANA) play minor roles in non-systemic JIA.¹⁸ On the other hand, the pathogenesis of ERA is driven by HLA-B27 mediated presentation of arthritogenic peptide after infections or barrier function disturbances.¹⁸ In ERA and psoriatic arthritis (PsA), the interplay between activated innate and adaptive immunity is dominated by IL-23 and IL-17 cytokines and the TNF pathway, which leads to chronic inflammation of the synovium in joints or entheses and subsequently results in bone damage.^{18,40} Overall, the pathogenesis and presentation of JIA is much more heterogeneous than rheumatoid arthritis (RA), and therefore JIA should not be merely viewed as the pediatric form of RA.³⁶

4. Diagnosis

JIA is characterized by chronic arthritis that persists for at least six weeks, with a clinical onset before 16 years of age.^{16,17} To accurately diagnose JIA, arthritis with other known etiologies should be excluded. Consensus statements on the diagnosis of JIA are presented in Table 3. The clinical characteristics of Taiwanese JIA patients according to the seven ILAR JIA subtypes are summarized in Table 4.^{2,5,41,42} In the assessment of JIA, musculoskeletal ultrasonography is a useful non-invasive and sensitive tool that can assist in evaluation of disease activity and subtype classification, as it can detect synovium hypertrophy, joint effusion, increased blood flow by power Doppler, tendon/-bursae inflammation, or enthesitis.⁴³ Imaging with magnetic resonance imaging (MRI) may be helpful in detecting affected joints or bone lesions that are not clinically apparent.

5. Treatment

5.1. Pharmacological therapy for JIA: General principles

Consensus statements on the treatment of JIA are presented in Table 5. It is important to start treatment early, and achieve the main goals of controlling inflammation, minimizing tissue damage, and also monitoring and treating JIA-related comorbidities such as uveitis or inflammatory bowel disease (IBD). It is essential for patients to undergo regular check-ups at a specialized clinic led by a pediatric rheumatologist every 1–3 months, in order to ensure treatment safety and monitor disease activity. Considering that different JIA subtypes may be driven by differing mechanisms, independent treatment algorithms have been developed for different subtypes, and are presented in Figs. 3–6. In terms of treatment response, “adequate response” is defined as at least 30% improvement from baseline in at least two of the following parameters, with no parameters showing more than 30% deterioration: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), number of joints with active arthritis, number of joints with limitation of movement, and physician-evaluated global assessment score. “Intolerance” is defined as inability to tolerate the side effects of certain medications, such as severe bone marrow suppression, etc. In most cases, step-up treatment should be considered if there is an inadequate response after 3 months of treatment. However, if the patient’s condition deteriorates during the first month of treatment, earlier step-up treatment could be considered.

Table 1
Consensus statements regarding the characteristics of JIA.

1. JIA is a complex and heterogeneous disease, and different subtypes have varying pathological mechanisms; therefore, treatment strategies should be tailored to the disease subtype.
2. In Taiwan, ERA is the predominant JIA subtype.
3. JIA is more heterogeneous than rheumatoid arthritis (RA), and therefore JIA should not be simply viewed as the pediatric form of RA.

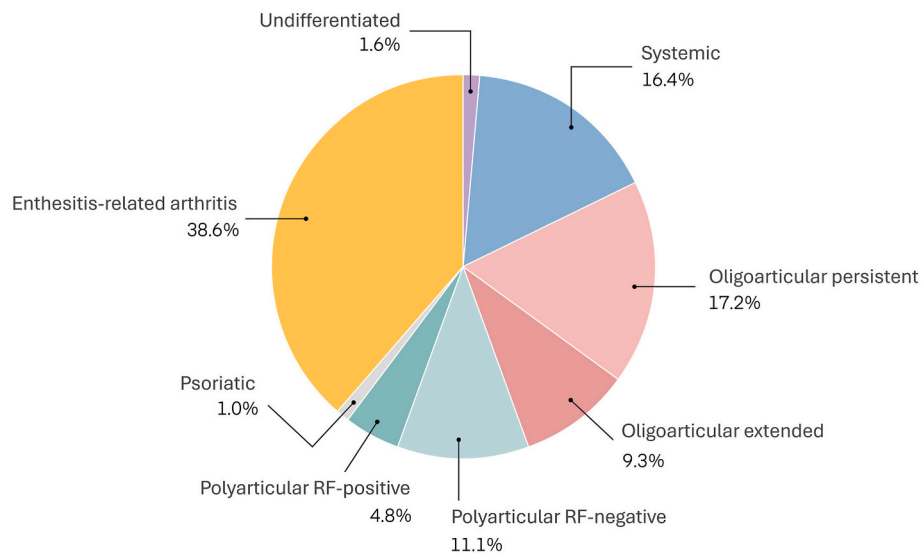


Fig. 1. Distribution of JIA subtypes in Taiwan. Results were pooled from two independent surveys of JIA patients (n = 378) conducted at two tertiary medical centers. RF, rheumatoid factor.

Table 2

Comparison of JIA epidemiology in Taiwan and other countries.

Subtype	Proportion of all cases (%)				Age of onset (years)		Ratio (Girls: Boys)	
	Taiwan ^{5,13}	Japan ⁷	Europe ⁹	US ¹¹	Taiwan ^{5a}	International ^{15,16}	Taiwan ⁵	International ^{15,16}
Systemic	16.4	8~50	8.2	9	5~11	1~5	1.8 : 1	1 : 1
Oligoarticular	26.5	N/A	55.2	48	3~12	2~4	1.1 : 1	3 : 1
Persistent	17.2	10~40	N/A	N/A	4~10	N/A	1.1 : 1	N/A
Extended	9.3	0~10	N/A	N/A	3~12	N/A	1.2 : 1	N/A
Polyarticular RF-negative	11.1	10~30	14.0	31	4~12	2~4 and 10~14	1.9 : 1	3 : 1 and 10 : 1
Polyarticular RF-positive	4.8	10~35.3	2.0		9~14	Adolescence	See note ^b	9 : 1
Psoriatic	1.0	0~5.9	3.6	8	6~11	2~4 and 9~11	1 : 2	2 : 1
ERA	38.6	0~14	N/A	N/A	9~12	9~12	1 : 5.6	1 : 7
Undifferentiated	1.6	0~4	16.9	4	9~15	Varies	4 : 1	N/A

N/A, not available; RF, rheumatoid factor; US, United States.

^a Numbers represent interquartile range (IQR), and have been rounded up.

^b All (n = 17) polyarticular RF-positive patients identified in the survey were girls, and thus it was not possible to evaluate the sex ratio for this subtype.

The treatment algorithm for oligoarticular JIA (1–4 joints involved) is presented in Fig. 3, and the first choice for treatment is a non-steroidal anti-inflammatory drug (NSAID) or injection of intra-articular glucocorticoids (GCs; e.g. triamcinolone hexacetonide) into large joints, similar to the corresponding 2021 ACR guideline recommendations.⁴⁴ For those with inadequate response or intolerance to NSAID therapy, the second choice of treatment is a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD). Methotrexate (MTX) is preferred, followed by sulfasalazine (SSZ), hydroxychloroquine (HCQ) or leflunomide (LEF). A biologic disease-modifying anti-rheumatic drug (bDMARD), such as a tumor necrosis factor- α (TNF- α) inhibitor or anti-interleukin-6 receptor (IL-6R) therapy, or a targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD), such as a JAKi, can be considered for extended oligoarticular patients. For those with poor prognostic factors, such as involvement of the ankle, wrist, hip, or temporomandibular joints, or bone erosion, rapid escalation of treatment should be considered to achieve better disease control.

The treatment algorithm for polyarticular JIA (5 or more joints involved) is presented in Fig. 4, and the first choice of treatment is a csDMARD in combination with an NSAID, similar to the corresponding

2019 ACR guideline recommendations.⁴⁵ MTX is the csDMARD of choice, followed by SSZ and LEF. Short-term systemic GCs can be considered in the initial acute stage, but should not be given for more than three months due to the risk of undesirable side effects. In case of inadequate response or intolerance to treatment, a bDMARD, such as a TNF- α inhibitor (e.g. adalimumab or etanercept) or an anti-IL-6R therapy (e.g. tocilizumab), or a tsDMARD such as JAKi can be considered. If symptoms persist after treatment or there is intolerance, switching to another bDMARD with a different mechanism of action should be considered; for example, a TNF- α inhibitor may be switched to anti-IL-6R, anti-CD28 (abatacept), or a JAKi.

The treatment algorithm for ERA is shown in Fig. 5. Based on whether there is axial involvement or not, treatment recommendations differ. In cases with non-axial involvement, an NSAID in combination with or without a csDMARD remains the first-choice treatment, similar to the corresponding 2019 ACR guideline⁴⁵ and 2022 GJKR guideline⁴⁶ recommendations. If axial joints (e.g. the sacroiliac joints) are involved, or if there is inadequate response or intolerance to first-line treatment in cases with non-axial involvement, a bDMARD, such as a TNF- α inhibitor or IL-17A inhibitor, or a tsDMARD such as JAKi is suggested. If there is

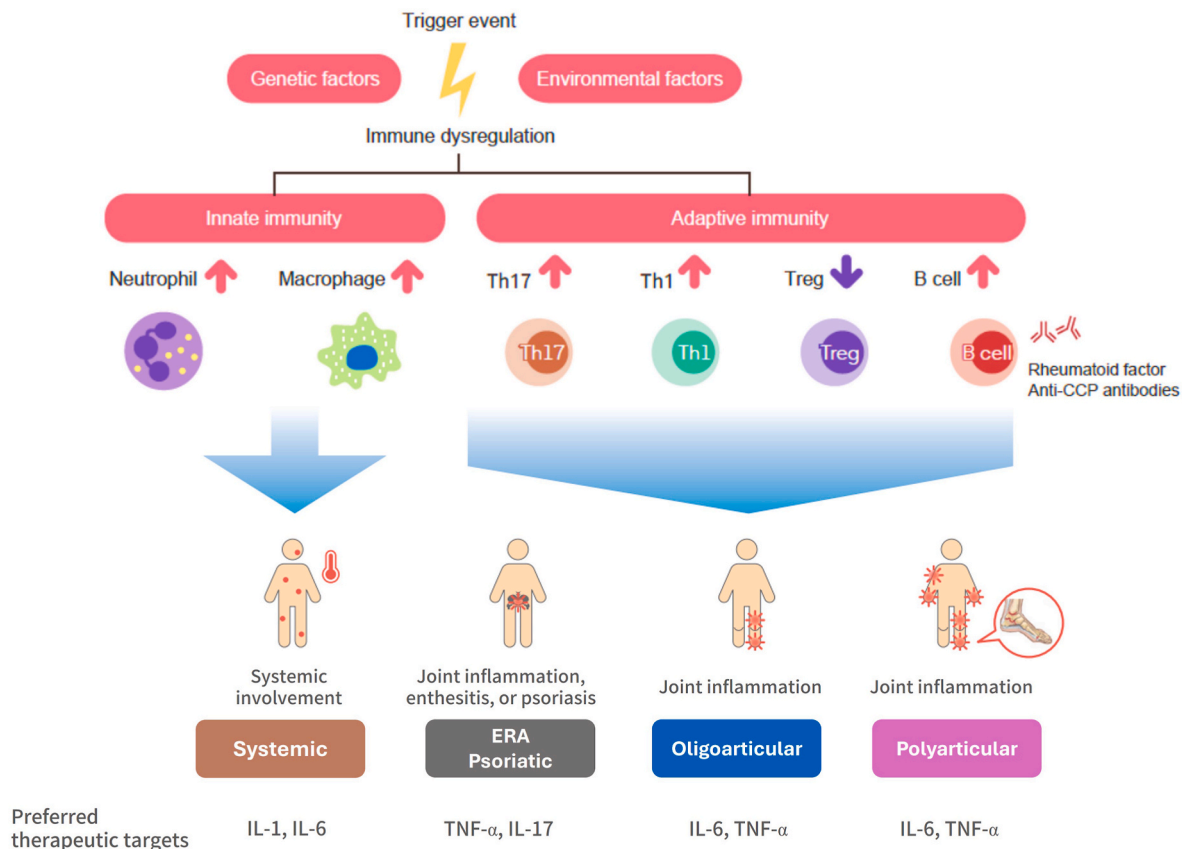


Fig. 2. Current conceptual schematic of JIA pathogenesis. Anti-CCP antibodies; anti-cyclic citrullinated peptide antibodies; IL, interleukin; Th, helper T cell; TNF- α , tumor necrosis factor- α ; Treg, regulatory T cell.

Table 3

Consensus statements regarding the diagnosis of JIA.

1. Diagnosis of JIA requires comprehensive clinical assessment, including symptoms and signs, physical examination, laboratory and/or image studies, and exclusion of other conditions mimicking JIA.
2. Early referral to a pediatric rheumatologist is advised for patients with chronic arthritis or fever of unknown origin.

inadequate response or intolerance to treatment, another bDMARD with a different mechanism of action, or a JAKi, should be considered.

The treatment algorithm for systemic JIA is shown in Fig. 6, with the first choice of treatment being systemic GCs or a bDMARD, in combination with or without an NSAID. For bDMARDs, anti-IL-6R (e.g. tocilizumab), IL-1 β inhibitors (e.g. canakinumab), or IL-1R antagonists (IL-1Ra; e.g. anakinra) are preferred. If symptoms persist or there is intolerance to treatment, a csDMARD can be added. If arthritis persists, a bDMARD with another mechanism of action can be considered, preferably a TNF- α inhibitor or abatacept.

Of note is that macrophage activation syndrome (MAS) may occur in patients with systemic JIA.⁴⁷ The symptoms and signs of MAS include persistent fever, bleeding tendency, hepatosplenomegaly, jaundice, central nervous system (CNS) dysfunction, and multiple organ failure.^{42,47,48} Typical laboratory features include leukopenia, thrombocytopenia, decreased levels of ESR and fibrinogen, and increased levels in ferritin, liver enzymes, lactate dehydrogenase (LDH), triglycerides, and D-dimer.^{42,47,48} Hemophagocytosis can be seen in bone marrow biopsy results.⁴⁵ Mortality in MAS is around 8–20%.⁴⁷ The treatment algorithm for systemic JIA with MAS remains the same as that shown in Fig. 6, but intravenous immunoglobulin (IVIG) or etoposide can also be considered. In addition, the dose of systemic GCs can be higher, and the duration of treatment can be longer. However, the dose of systemic GCs should be tapered gradually after the acute stage, and abrupt discontinuation

should be avoided to prevent flare-up of inflammatory symptoms. Choosing and adjusting empiric immunomodulation for hemophagocytic lymphohistiocytosis (HLH)/MAS can be challenging. There is no consensus on the optimal medication regimen, except that GCs are recommended as the main treatment. According to the 2022 European Alliance of Associations for Rheumatology (EULAR)/ACR points to consider for the management of suspected HLH/MAS management,⁴⁹ empiric immunomodulation with GCs, IL-1RA anakinra, and/or IVIG is recommended. The dose of GCs ranges from standard dose (1–2 mg/kg/day) to high-dose (10–30 mg/kg/day, max 1 g/day for 1–3 days). IVIG is given as 1 g/kg/day for 2 days or 0.4–1 g/kg/day for 2–5 days.⁴⁹ For patients with increasing inflammation and/or worsening organ damage despite early immunomodulation, treatment escalation with higher doses of GC and/or alternative agents should be considered.⁴⁹ These alternative agents include etoposide, ciclosporin, ruxolitinib, emapalumab, and rituximab.⁴⁹

5.2. Role of NSAIDs in JIA

NSAIDs can effectively alleviate pain and are generally well-tolerated, with major side effects including gastrointestinal discomfort and indigestion, and rarely but critically, kidney injury. Celecoxib, although similar to naproxen in efficacy and safety, is not approved for children and adolescents.⁴⁵ If NSAIDs are used continuously for over one

Table 4

Clinical and laboratory characteristics of JIA patients in Taiwan according to the seven ILAR JIA subtypes.

Subtype	Extra-articular manifestations; Family history	Laboratory features
Systemic	Fever (100%), arthritis (89.3%), evanescent skin rashes (67.9%), lymphadenopathy (46.4%), hepato-splenomegaly (21.4%), serositis (7.1%), uveitis (3.6%)	ANA(+) (7.1–27%), RF(+) (0–8%), leukocytosis, thrombocytosis, elevated ESR, CRP, ferritin (71.4%), LDH (90.9%), ALT (33.3%), hemophagocytosis in bone marrow aspiration or biopsies (11.5%)
Oligoarthritis Persistent Extended	Uveitis (9.4%) Uveitis (7.7%)	RF(–), elevated ESR, CRP ANA(+) (46.9%) ANA(+) (15.4%)
Polyarthritis RF-negative	Chronic uveitis (10%), growth retardation	ANA(+) (34.8%), RF(–), elevated ESR, CRP, mild anemia
Polyarthritis RF-positive	Rheumatoid nodule (10%)	ANA(+) (77.8%), RF(+), elevated ESR, CRP, mild anemia
Psoriatic	Psoriasis, dactylitis, nail pitting, onycholysis	ANA(+) (66.7%), elevated ESR, CRP, mild anemia
ERA	Enthesitis, acute uveitis (9.6–10%), inflammatory bowel disease; positive family history (11%)	HLA-B27(+) (82.2–97%), ANA(+) (27.4%)
Undifferentiated		ANA(+) (20%)

ALT, alanine aminotransferase; ANA, anti-nuclear antibodies; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase.

month with no improvement, they should not be used alone for treatment.⁵⁰

5.3. Role of systemic GCs in JIA

Systemic GCs are recommended as bridging therapy (duration <3 months) during the initiation or escalation of primary treatment, when JIA is still highly active.⁵¹ Systemic GCs can also be used in JIA with systemic features and polyarticular involvement before DMARDs take full effect.

5.4. Role of intra-articular GCs in JIA

Injections of crystalloid glucocorticoid solution into large joints are effective and rarely incur complications, making this a frontline treatment for oligoarticular JIA.⁴⁴ Injections of the same joint should be spaced at least three months apart. Reports suggest that about 2% of cases may experience local fat tissue necrosis, but with aseptic techniques, infection risk is low.⁵¹ Triamcinolone hexacetonide has longer-lasting effects than triamcinolone acetonide.^{51,52}

Table 5

Consensus statements regarding the treatment of JIA.

1. NSAIDs can be used to alleviate active arthritis symptoms across all JIA subtypes, either as initial or adjunctive therapy. Intra-articular glucocorticoid injection to treat arthritis in large joints can also be considered for oligoarticular JIA.
2. Conventional synthetic DMARDs, in particular MTX, are recommended to treat JIA with inadequate response or intolerance to NSAIDs.
3. Biologic DMARDs (e.g. TNF- α inhibitors or anti-IL-6R) or tsDMARDs (e.g. JAKi) in combination with MTX are recommended if there is an inadequate response or intolerance to csDMARD therapy in polyarticular JIA. TNF- α inhibitors, IL-17A inhibitors, or JAKi may be considered for ERA and psoriatic arthritis, while anti-IL-6R and IL-1 inhibitors are suggested for systemic JIA.
4. For ERA with peripheral arthritis, SSZ or MTX is recommended; however, a bDMARD (e.g. TNF- α inhibitors or IL-17A inhibitors) is preferred if axial joints are involved (suggestive of poor prognosis).
5. Short-term systemic glucocorticoids are recommended as bridging therapy for high disease activity, especially when there are systemic features or polyarticular involvement.
6. Risk management plans should be in place before initiating bDMARD and tsDMARD therapy.

5.5. Role of csDMARDs in JIA

MTX is the preferred csDMARD for JIA, as it can increase treatment response achievement rates, and can be administered orally or subcutaneously with comparable efficacy.⁵³ MTX has good efficacy with an acceptable safety profile, and serious adverse events occur in less than 1% of patients.^{53–55} Folate supplementation can reduce the incidence of MTX-associated hepatotoxicity and gastrointestinal side effects.⁵⁶ Other csDMARDs, including SSZ, HCQ, and LEF, are considered only if MTX is ineffective or intolerable for most JIA subtypes. Based on evidence from adult-onset spondyloarthritis, SSZ is likely to benefit ERA patients with peripheral arthritis.⁵⁷

5.6. Role of bDMARDs in JIA

Following advancements in understanding the pathogenesis of JIA, targeted biologic agents including bDMARDs and tsDMARDs have rapidly expanded in recent decades. These agents selectively inhibit cytokines, cytokine receptors, or directly bind to lymphocyte receptors such as CD28, as summarized in Fig. 7. This class of therapeutics includes both antibodies and fusion proteins, which can be administered either subcutaneously or intravenously. As shown in Fig. 3–6, bDMARDs are recommended for patients who inadequately respond to or cannot tolerate csDMARDs. Specifically, TNF- α inhibitors and anti-IL-6R therapies are recommended for extended oligoarticular and polyarticular JIA (Fig. 4); TNF- α inhibitors and IL-17A inhibitors are recommended for ERA and psoriatic arthritis (Fig. 5); and anti-IL-6R and IL-1 blockade are recommended for systemic JIA (Fig. 6). If a patient is initiated on TNF- α inhibitors but responds inadequately or is intolerant to treatment, it is recommended to use another bDMARD that targets other inflammatory cytokines or pathways.⁴⁵ The concomitant use of MTX is recommended in adalimumab treatment to reduce the risk of neutralizing antibody production.^{45,58} In the treatment of JIA-associated uveitis, adalimumab has been shown to be effective in several clinical studies, while the evidence is limited for most other bDMARDs.^{59,60}

5.7. Role of tsDMARDs in JIA

JAKs are intracellular enzymes that transmit signals generated by cytokines and receptors on the cell membrane into the cell, subsequently promoting the phosphorylation and activation of signal transduction and transcriptional activators (STATs) to affect the function of hematopoietic cells and immune cells. JAKi can directly enter the inner layer of inflamed cells, inhibit JAK, and regulate signal transduction triggered by inflammatory cytokines. To date, tofacitinib, a JAKi mainly targeting JAK1 and JAK3, has been shown to be effective in treating polyarticular JIA⁶¹; and baricitinib, a selective JAK1/JAK2 inhibitor, has been shown to be effective against polyarticular JIA, ERA, psoriatic arthritis and extended oligoarticular JIA.⁶² However, in large clinical trials, abnormalities in lymphocytes, decreases in neutrophils, anemia, elevated liver enzymes, and increased blood lipids have been shown in patients receiving JAKi. These treatments may also increase the risk of infections (e.g. upper respiratory infections) and herpes virus

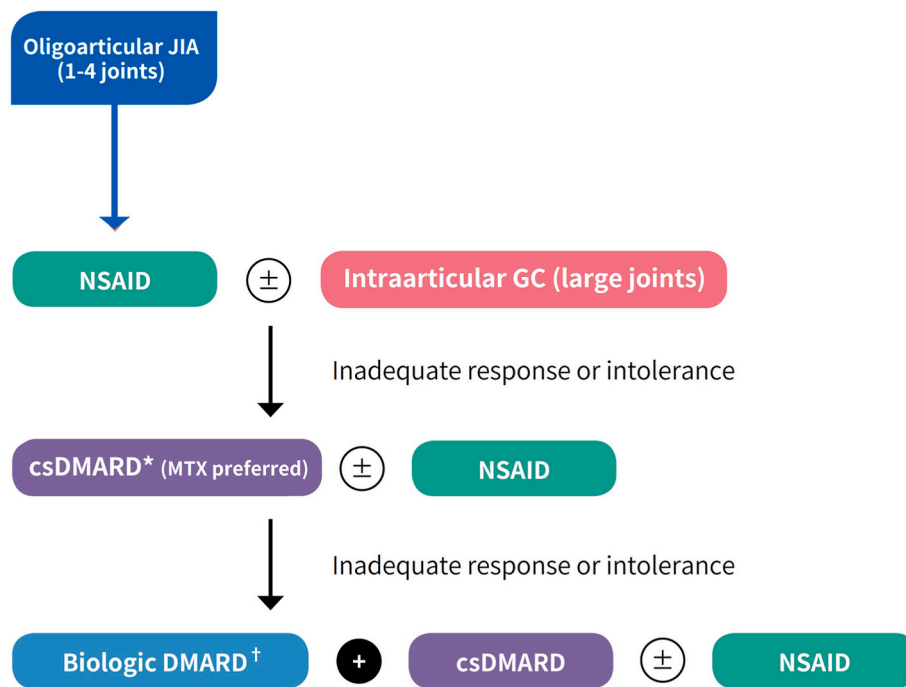


Fig. 3. Treatment algorithm for oligoarticular JIA. *Methotrexate (MTX) is the preferred csDMARD, followed by sulfasalazine, hydroxychloroquine, or leflunomide. †For bDMARDs, TNF- α inhibitors or anti-IL-6R are suggested; JAKi can also be considered.

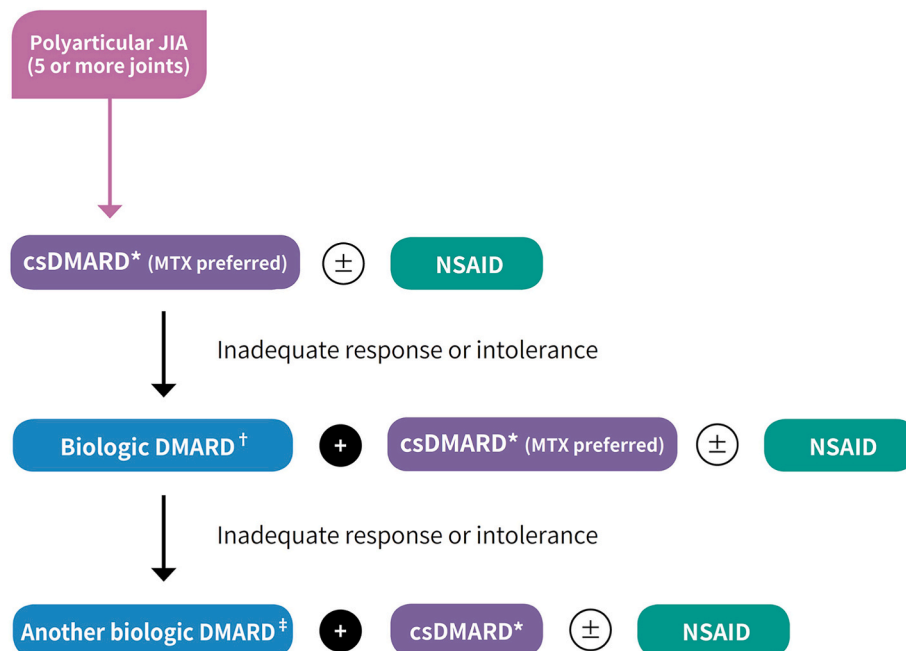


Fig. 4. Treatment algorithm for polyarticular JIA. *Methotrexate (MTX) is the preferred csDMARD, followed by sulfasalazine or leflunomide. †For bDMARDs, TNF- α inhibitors or anti-IL-6R are suggested; JAKi can also be considered. ‡Consider switching to a bDMARD with a different mechanism, or a JAKi.

reactivation.^{61–63} In addition, the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have added boxed warnings to the approved product labels for JAKi, highlighting potential serious adverse effects (SAEs) such as cardiovascular events, cancer, thrombosis, and risk of death. Although there have been no reports of such SAEs among JIA patients as yet, the potential risks of treatment among young patients should be considered when prescribing JAKi.

5.8. Risk management plans in the treatment of JIA

Although bDMARDs and tsDMARDs have excellent therapeutic effects, there are concerns about the risk of viral hepatitis (such as hepatitis B or C) reactivation and increased risk of latent tuberculosis infection reactivation while on treatment.⁶⁴ Therefore, since April 2012, the Taiwan Food and Drug Administration (TFDA) has announced that risk management plans should be in place when initiating bDMARDs or tsDMARDs. As part of risk management, all patients should undergo

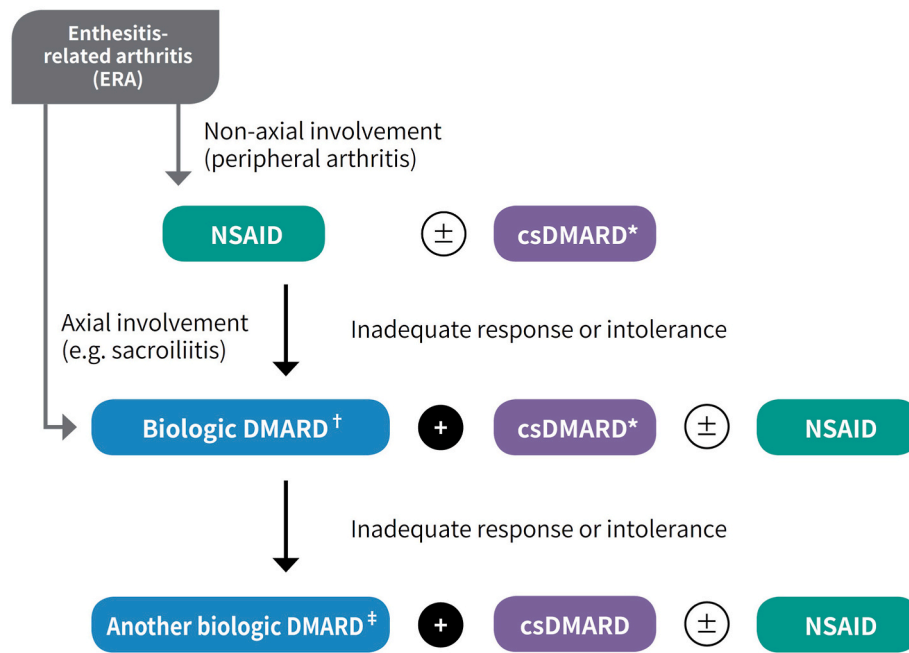


Fig. 5. Treatment algorithm for ERA. *For csDMARDs, SSZ or MTX can be considered. [†]For bDMARDs, TNF- α inhibitors or IL-17A inhibitors are suggested; JAKi can also be considered. [‡]Consider switching to a bDMARD with a different mechanism, or a JAKi.

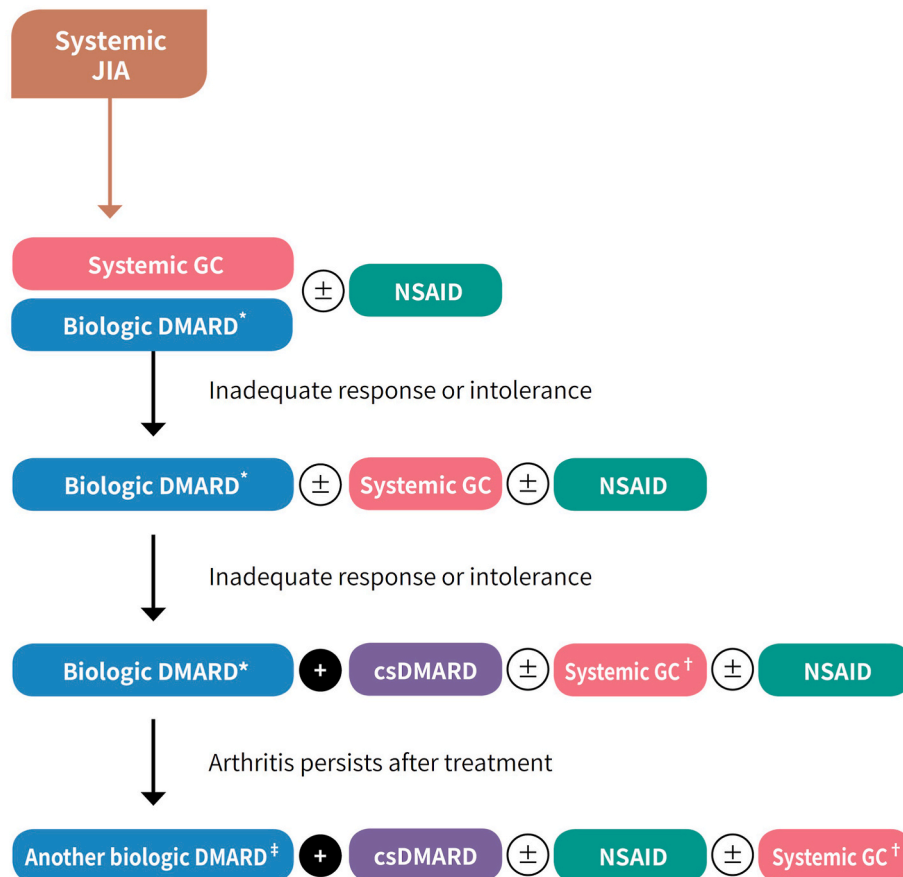


Fig. 6. Treatment algorithm for systemic JIA. *For bDMARDs, anti-IL-6R, IL-1 β inhibitors, or IL-1R antagonists are preferred. [†]Consider switching to TNF- α inhibitors or abatacept for another bDMARD. [‡]The dose of systemic GCs should be gradually tapered, and abrupt discontinuation should be avoided.

Mechanism of action	Drug	Approved indications in JIA (Up to October 2024)																	
		Systemic			Polyarticular RF-positive			Polyarticular RF-negative			Extended oligoarticular			ERA			Psoriatic		
		TFDA	FDA	EMA	TFDA	FDA	EMA	TFDA	FDA	EMA	TFDA	FDA	EMA	TFDA	FDA	EMA	TFDA	FDA	EMA
TNF- α inhibitors	Etanercept				2	2	2	2	2	2			2			12			12
	Adalimumab ^a				2	2	2	2	2	2						6			
	Golimumab					2	2		2	2								2	
	Certolizumab pegol					2			2										
IL-1 β inhibitors	Canakinumab		2	2															
IL-1Ra	Anakinra ^b			8m															
Anti-IL-6R	Tocilizumab	2	2	1	2	2	2	2	2	2									
	Sarilumab					2 ^c			2 ^c										
IL-17A inhibitors	Secukinumab												2	6	2	6	6	2	6
IL-12/23 inhibitors	Ustekinumab																	6	
Anti-CD28	Abatacept				6	2	2	6	2	2								2	
JAKi	Tofacitinib				2	2	2	2	2	2									2
	Baricitinib				2		2	2		2	2		2	2		2	2		2
	Upadacitinib					2 ^d			2 ^d									2 ^d	

Fig. 7. Currently available bDMARDs and tsDMARDs in Taiwan with approved indications for JIA. The approving agencies are labeled in different colors. Numbers in the squares indicate the earliest age (in years; except where indicated as m, months) for which the indication was approved. ^aAdalimumab has a high risk of developing neutralizing antibodies, but for JIA patients with uveitis, it serves as the treatment of choice. ^bAnakinra has a high risk of developing anti-drug antibodies, but this appears to have a limited impact on efficacy. ^cPatients must have active polyarticular JIA and weigh 63 kg or greater. ^dAvailable in the United States for patients with an inadequate response or intolerance to one or more TNF blockers. EMA, European Medicines Agency; FDA, United States Food and Drug Administration; TFDA, Taiwan Food and Drug Administration.

comprehensive screening and assessment for tuberculosis and viral hepatitis prior to initiating treatment.

5.9. Non-pharmacologic treatment for JIA

In the acute stage of JIA, ice packing may attenuate pain, while in the chronic stage, joint extension exercises, massage, hot packing, and splinting may serve to prevent joint contracture. Exercise is recommended for JIA patients, particularly low weight-bearing exercises such as swimming, and the appropriate type and duration of exercise should be discussed with physicians. Surgery is suggested for joint contractures. Patients should seek to achieve a balanced diet, and avoid special diets, immunostimulants, or supplements with no clinical evidence of benefit. There is currently no evidence that complementary and alternative medicine, such as acupuncture, can provide consistent benefit against JIA.

6. Monitoring and prognosis

Consensus statements on monitoring in JIA are presented in Table 6. Because the course of JIA involves dynamic changes, joint deformities, joint flexion contractures, height impacts, and extra-articular complications, and due to the risk of side effects when undergoing long-term drug treatment, regular follow-up and monitoring is very important. The ACR20, ACR Pedi30, and the Juvenile Arthritis Disease Activity Score (JADAS) are simple disease assessment scores that are widely used

in clinical practice.⁶⁵ The Wallace criteria⁶⁶ is also helpful for conducting the necessary evaluation of disease relief in patients on treatment, as well as to assess whether medication should be adjusted or eventually stopped.

Follow-up visits are generally recommended at intervals of 1 week to 1 month during the acute phase. Once the patient is stabilized, follow-up intervals can be extended to every 1–3 months. At each follow-up visit, symptoms and functional status should be assessed, including the number and location of affected joints; the degree of pain, redness, swelling, and morning stiffness; the impact on daily activities, such as exercise, walking, and running; and the presence of extra-articular symptoms, such as rash or fever. A detailed physical examination should be performed at each visit. Laboratory tests, such as CRP and/or ESR for monitoring disease activity, liver and kidney function tests, and a complete blood count (CBC), should be performed as appropriate depending on the medications prescribed. In addition to diagnostic imaging (e.g., ultrasound, X-ray, or MRI), imaging follow-up is recommended every 1–2 years during treatment. Ultrasound is now widely used for the early detection of disease-related changes.

The most common extra-articular manifestation of JIA is uveitis. In Taiwan, the reported prevalence of uveitis is about 4.7–6.7%, and 84% of cases occur within four years after JIA diagnosis.⁴¹ It is recommended that JIA patients should receive regular follow-up in the ophthalmology clinic.⁶⁷ The severity of uveitis is not related to the severity and activity of arthritis; however, patients under six years of age, girls, ANA-positive patients, and those with oligoarticular or polyarticular RF-negative

Table 6

Consensus statements regarding the monitoring of JIA.

1. Long-term monitoring of the side effects of JIA pharmacologic treatment is needed.
2. Referral to an ophthalmologist for evaluation and follow-up of uveitis is strongly recommended.
3. Monitoring and follow-up of extra-articular manifestations and co-morbidities is recommended.

subtypes within four years of onset are at high risk. Once JIA is diagnosed, the patient should be referred for an eye examination.⁶⁷ High-risk groups should undergo ocular examination every 3–6 months, while low-risk groups should have regular annual examination.^{14,67} Once the diagnosis is established, follow-up intervals should be determined by the ophthalmologist. Patients should be instructed to regularly self-monitor for any photophobia, pain, or vision loss.

The overall prognosis of JIA is better than that of adult RA. The long-term prognosis depends on several factors, including response to drug treatment, joint damage and functional impairment, disease duration, age at remission, psychosocial impact, and presence of comorbidities.

Before the introduction of bDMARDs, up to 50% of patients with JIA had active disease persisting into early adulthood.¹⁴ The greater the disease severity, the more medications are typically required, even with the use of bDMARDs. However, treatment with bDMARDs has been shown to improve height growth in JIA patients. In Taiwan, a total of 104 JIA patients were followed for 12 years, and approximately one-third achieved catch-up growth after 12 months of bDMARD treatment.⁶⁸ bDMARD therapy represents a significant milestone in JIA management.

Once joint damage and functional impairment have occurred, full recovery is often no longer achievable, even with treatment. Aggressive rehabilitation, and even surgery in some cases, may be required. Physicians should take early preventive measures to avoid such complications.

In oligoarticular JIA, a relatively higher proportion of patients achieve remission compared to other subtypes. A 15-year follow-up study of Taiwanese patients receiving treatment showed that disease activity persisted in 15% of patients with persistent oligoarticular JIA and in 38.5% of those with extended oligoarticular JIA.⁵ Therefore, in this oligoarticular subtype, prognosis largely depends on whether the disease progresses to the extended form.⁶⁹

In Taiwan, studies on polyarticular RF-negative JIA have reported that disease activity remains despite treatment in approximately 40% of patients.⁵ Early onset, the presence of anti-CCP antibodies, subcutaneous rheumatoid nodules, and hip or wrist joint involvement are indicators of poor prognosis.

Sacroiliac joint involvement is also a poor prognostic factor in ERA, the most common type of JIA in Taiwan.¹³ Therefore, early and aggressive treatment, including bDMARDs, is recommended. However, a recent study in Taiwan has shown that temporomandibular joint (TMJ) involvement is associated with a poorer response to TNF- α inhibitors, such as adalimumab.⁷⁰

Data from the Taiwan National Health Insurance Research Database indicate that the incidence rate of uveitis among JIA patients is 8.3 per 1000 person-years.⁷¹ Furthermore, the use of bDMARDs did not significantly alter the risk of uveitis compared to patients who did not receive bDMARDs.⁷¹

Notably, disease progression varies among different JIA subtypes. The course of systemic JIA, in particular, is often unpredictable.⁷² In general, the mortality rate is low, except in cases complicated by MAS.⁷² The prognosis for patients with PsA is uncertain but is generally worse than that of polyarticular JIA.⁶⁹

7. Patient and family education

JIA is a chronic disease that requires long-term care. Patients and their parents play crucial roles in the treatment team and should be aware of several important considerations.⁷³ As mentioned above, non-pharmacologic treatments, such as proper nutrition and regular exercise, are essential.⁷³ Adherence to treatment and following medical advice is important, including taking prescribed medications as directed and attending follow-up visits as scheduled.⁷³ Self-monitoring by keeping a daily record of joint activity, including the degree of pain, number and location of affected joints, and any changes in symptoms, can be useful.⁷³ If extra-articular symptoms occur, such as fever, rash,

photophobia, or eye discomfort, the patient should return to the clinic immediately.⁷³ Psychosocial care is also important. Patients should be encouraged to participate in daily activities under the guidance of their physician. Family members play a vital role in helping reduce the anxiety associated with the unpredictable nature of the disease.⁷³ With regard to vaccination, live vaccines such as the measles-mumps-rubella (MMR) vaccine are generally not administered during immunosuppressive therapy.⁷⁴ The administration of live or inactivated vaccines should be evaluated by pediatric rheumatologists.⁷⁴

8. Future directions and research

While the ILAR classification remains the most widely adopted system worldwide, its high heterogeneity within categories and the challenge of bridging childhood-onset and adult forms of arthritis have driven the development of new classification systems for JIA. In 2019, the Pediatric Rheumatology International Trials Organization (PRINTO) International Consensus proposed a revised framework that defines JIA as arthritis persisting for more than six weeks with an onset before the age of 18 years,⁷⁵ comprising six subtypes: systemic; early-onset ANA-positive; RF-positive; enthesitis/spine inflammation-related; other types; and unclassified arthritis. However, the PRINTO classification does not demonstrate improved alignment with clinico-biologic subtypes or adult forms of arthritis compared to the ILAR classification. Therefore, the search for a more refined and clinically meaningful classification system remains necessary.

Meanwhile, the treatment landscape for JIA has advanced significantly in recent decades. In addition to approved bDMARDs and tsDMARDs summarized in Fig. 7, several emerging therapeutic approaches leveraging precision medicine to target specific pathogenic molecules are currently under investigation (Supplementary Table 1). IL-17 signaling inhibitors are under evaluation for ERA; IL-17A, IL-17F, IL-23, TYK2, and PDE4 inhibitors are being tested for juvenile psoriatic arthritis; and JAK inhibitors are being explored for systemic JIA. Recently, emapalumab, a monoclonal antibody targeting interferon- γ , was approved for MAS associated with adult-onset Still's disease and systemic JIA.⁷⁶ Given the elevated free IL-18 concentrations in MAS, recombinant IL-18 binding proteins or monoclonal antibodies may also offer therapeutic benefits.⁷⁷

9. Conclusion

This TAPAAI guideline for the diagnosis and management of JIA provides a comprehensive summary of the latest evidence, guidelines, and expert opinion regarding the diagnosis, treatment, and monitoring of JIA, and is intended to serve as a practical reference for healthcare professionals in managing this heterogeneous and complex disease. With the advent of new treatments such as bDMARDs and tsDMARDs, it is hoped that the long-term adverse impacts of JIA can be mitigated, and that patient outcomes can continue to improve.

CRedit authorship contribution statement

Hai-Lun Sun: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yu-Hsuan Kao:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Hsin-Hui Yu:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Li-Chieh Wang:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Chao-Yi Wu:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. **Tsung-Chieh Yao:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

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