

Current Review of Systemic Juvenile Idiopathic Arthritis: What Do Paediatricians Need to Know?

Asma R. Albaker

Paediatrics Department, College of Medicine, King Saud Medical City; and King Saud University, Riyadh, Saudi Arabia

Email: asma.albaker@ksu.edu.sa

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Abstract

Systemic juvenile idiopathic arthritis is classified as an autoimmune entity and a subtype of juvenile idiopathic arthritis, although it has many features of autoinflammatory-type of diseases. This review article will elaborate on the disease's pathogenesis and its proposed relation to autoinflammatory diseases including defective innate immunity and phagocytosis response leading excessive cytokine release. It also explains the disease's epidemiology, clinical phenotype, diagnostic challenges, complications and current advancements in the treatment of systemic juvenile idiopathic arthritis, such as IL-1 and IL-6 antagonists and their impact on the disease trajectory. Care of patients with systemic juvenile idiopathic arthritis requires a comprehensive multidisciplinary team to optimize the care and avoid complications of the disease itself such as growth impairment, macrophage activation syndrome or the complications of immunosuppressant and immunomodulatory treatments.

Keywords

Juvenile Idiopathic Arthritis, Systemic Juvenile Idiopathic Arthritis, Autoinflammatory, Arthritis, Biologics

1. Introduction

Systemic juvenile idiopathic arthritis (sJIA) is a distinctive subtype of juvenile idiopathic arthritis (JIA), which is considered a systemic arthritis subtype according to the classification provided by the International League of Associations for Rheumatology (ILAR) [1]. Various names and nomenclatures, including systemic juvenile rheumatoid arthritis, systemic juvenile chronic arthritis,

systemic-onset JIA and childhood-onset Still's disease, have been used to describe this condition, but sJIA is the preferred descriptive terminology [1]. Adult-onset Still's disease (AOSD) is a continuum of sJIA with similar pathophysiological and immunological characteristics, clinical phenotype, pharmacological response and epidemiological characteristics, such as a lack of sex predilection, except for the age of onset [2] [3]. The clinical definition of the systemic arthritis subtype in accordance with the ILAR classification includes 2-week duration of fever and arthritis as cardinal features, as well as at least one of the following: hepatosplenomegaly, lymphadenopathy, serositis or typical rash [1]. Diagnosis is based largely on the identification of clinical criteria and exclusion of other serious conditions that mimic its symptoms, such as infection and malignancy [4]. Early recognition of sJIA and initiation of proper treatment are considered critical to successfully controlling inflammation and disease, as well as potentially reducing long-term morbidity and mortality, particularly given the growing evidence of the benefit of biologic disease-modifying antirheumatic drugs (DMARDs) early in the course of the disease [5] [6] [7].

This review article will explore the most recent research on this disorder, mainly on the disease's epidemiology, pathogenesis, clinical phenotype, laboratory tests, complications and treatment of sJIA. The last section will review all aspects of caring for patients with sJIA that a paediatrician should know as well as supervising the care collaboratively with patients, families and other physicians and allied healthcare workers.

2. Objectives

After completing this article, the reader should attain the following goals:

- 1) Understand the pathophysiology of sJIA and its complication, macrophage activation syndrome (MAS);
- 2) Recognize the symptoms and signs of sJIA and exclude other mimickers;
- 3) Know the current treatment options and understand the treatment to target approach; and
- 4) Comprehensively care for patients with sJIA.

3. Methods

A literature review was conducted Jun. 1 2020 comprising all English articles from the 1970s onward in the MEDLINE/Pubmed database. Medical Subject Headings were used to search for JIA AND sJIA. Other supplemented words have been used, such as Still's disease and systemic juvenile rheumatoid arthritis. All types of articles were reviewed, and determining usability for this review depended on the level of evidence, relation to the topic of interest and whether updated knowledge was considered. RTC and observational studies, such as cohorts, case series and case reports, were reviewed and included. The following organizational publications were reviewed so as to draw a review consensus on how to diagnose and treat sJIA: the American College of Rheumatology (ACR) guidelines, the

Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus, the Pediatric Rheumatology International Trials Organizations (PRINTO) and other paediatric rheumatology groups' consensus.

4. Epidemiology

According to a recent systemic review, the prevalence of JIA was ranged from 3.8 to 400/100,000, with an sJIA prevalence of 0 - 8.6/100,000 [8]. Systemic JIA comprises 10% - 20% of all JIA cases [9] [10]. However, these statistics vary geographically. For instance, systemic JIA represented approximately 2.7% of a JIA cohort in Sweden, whereas it accounted for as many as 33% of JIA cases in Southeast Asia and even 50% in Japan [11] [12] [13] [14] [15]. The systemic JIA subtype proportion out of all JIA cases varied depending on how the data were collected and how many sites were involved; for example, single-centre studies in Saudi Arabia estimated that sJIA comprised 23% to 36% of all JIA cases, making it the most common subtype [12] [14]. However, sJIA represented only 17% in a population study of all paediatric rheumatology clinics in Oman, suggesting that it is the third most common subtype [15]. Although it can manifest at any age during childhood and adulthood, its incidence peaks between 1 and 5 years of age [10] [16]. It is the only subtype of JIA that has been shown to affect males and females in equal proportions [10] [16]. In addition, it affects all races, but the African Americans experience a higher burden of disease activity and persistent arthritis according to a recent CARRA cohort analysis [16].

5. Pathogenesis

Systemic JIA exhibits more autoinflammatory than autoimmune features, which calls into question the precision of classifying sJIA under the JIA umbrella [17]. Its autoinflammatory features include innate immunity dysregulation, aberrant macrophage and neutrophil activation, and the subsequent release of cytokines and inflammatory proteins such as interleukin-1 (IL-1); interleukin-6 (IL-6) and interleukin-18 (IL-18); and S100A8, S100A9 and S100A12 [17].

Dissecting the roles of these cells, proteins and mechanisms to develop a systemic arthritis model is complex and not fully understood. Natural killer cells play a regulatory role in sJIA, as indicated by a study in mice that underwent the blockade of natural killer cell-activating receptors, causing an exaggerated and uncontrolled inflammatory response and an sJIA-like disease [18]. IL-18 cytokine is thought to have an upregulatory effect on interferon gamma, which leads to natural killer cell exhaustion and dysfunction and plays an essential role in the development of MAS [19] [20]. The changing paradigm in the recent history of sJIA treatment has been made possible through the successful use of medications that cause IL-1 and IL-6 receptor blockades, which have led to a substantial clinical and laboratory improvement in patients with sJIA, as well as reduced blood gene profile dysregulation [21] [22]. Other proposed mechanisms of sJIA devel-

opment include defective and insufficient IL-10 production by B-lymphocytes, which led to chronic inflammation status in already interferon-(IFN γ) deficient mice that have sJIA [23]. Persistent neutrophil activation occurs in active sJIA, as evidenced by increased levels of S100 8/9 protein levels from stimulated neutrophils [24].

The lack of autoreactive T cells and autoantibodies in sJIA points to a very limited adaptive immune system role in the disease's development [17] [25]. The adaptive immunity role in sJIA is apparent as recent studies have shown intersections with other forms of JIA associated with the major histocompatibility complex class II locus on chromosome 6 and another susceptibility locus on chromosome 1 [26] [27]. T cells, especially regulatory T cells (Tregs) and T effector cells, are affected in sJIA cases and may play a role in its pathogenesis; Tregs, which express interleukin-17 A (IL-17A), are more commonly found in the blood of patients with an acute sJIA phase with high inflammatory markers than in patients with acute nonsystemic JIA and healthy controls [28]. Early initiation of IL-1 blockades apparently overrules and dampens IL-17 expression by Tregs [28].

Although the role of genetics in sJIA remains largely unclear and continues to evolve, recent studies using whole-exome sequencing have proven that some familial cases of sJIA demonstrate a monogenic mutation in the LACC1 gene, which encodes for the laccase domain-containing enzyme at a region on chromosome 13 [17] [29]. LACC1 gene variants have a regulatory effect on TNF and IL-17 during inflammation [30]. In addition, specific polymorphisms in the cytokine regulation gene sequence may be associated with increased risk of sJIA, although additional studies have debated these findings [25].

6. Recognizing Clinical Manifestations of Systemic Juvenile Idiopathic Arthritis

The ILAR defines sJIA as a quotidian fever with a 2-week duration, at least 3 days of consecutive fever and the presence of arthritis in children before their 16th birthday as cardinal features, along with one of the following: typical rash, hepatosplenomegaly, lymphadenopathy or serositis [1] (see **Table 1**). A significant proportion of patients do not have all of these criteria at the time of diagnosis [10] [16]. In a large North American cohort of 435 sJIA patients, 14% of those diagnosed with sJIA did not meet the ILAR criteria because they lacked the specified quotidian fever or arthritis [16]. Demographic features and disease activity were similar between those who met ILAR criteria and those who did not [16].

Very recently, a newer classification of JIA was published, and the proposed subtypes of JIA were changed to six distinctive subtypes: early-onset Antinuclear antibody-positive JIA, rheumatoid factor-positive JIA, enthesitis/spondylitis-related JIA, systemic arthritis, unclassified and others [31]. SJIA remained under JIA in the latest researchers' effort, but some authors still call for a shift to a separate entity that falls under the category of autoinflammatory disorders [32]. The former

Table 1. ILAR diagnostic criteria for systemic juvenile idiopathic arthritis, Edmonton 2001. Adapted from Petty, R., Southwood, T., Manners, P., Baum, J., Glass, D., Goldenberg, J., *et al.* (2001) International League of Associations for Rheumatology Classification of Juvenile Idiopathic Arthritis: Second Revision, Edmonton, 2001. *Journal of Rheumatology*, **31**, 390-392.

Arthritis in any number of joints, together with a fever of at least 2 weeks' duration that is documented to be daily (quotidian) for at least 3 days and is accompanied by one or more of the following:

- Evanescent (nonfixed) rash
- Generalized lymphadenopathy
- Enlargement of liver or spleen
- Serositis

Exclusion criteria:

- 1) Psoriasis in the index case or first-degree relative with psoriasis
 - 2) Arthritis in HLA-B27-positive males after the 6th birthday
 - 3) Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, acute anterior uveitis or first-degree relative with one of those conditions
 - 4) Presence of immune globulin M rheumatoid factor on at least two occasions at least 3 months apart
-

study also examined the consensus and acceptability of paediatric rheumatologists to change the definition of systemic JIA to be comparable to a version of Yamaguchi's criteria for AOSD with minor modifications [31]. The description of this newer definition is as follows: after excluding infection, malignancy, autoimmune diseases and monogenic autoinflammatory diseases, a fever of unknown origin that is daily and documented for at least 3 consecutive days (with the quotidian pattern described below) and reoccurs over a duration of at least 2 weeks with two major criteria or one major criterion and two minor criteria [31] (see Table 2). This newer adaptation, if it gets validated, will make arthritis an unnecessary criterion to diagnose sJIA [31].

Clinically, children with sJIA can be segregated into two phenotypes: systemic autoinflammatory with fever-predominate or arthritis-predominate features [33]. Cases of sJIA are defined as probable if arthritis has not yet developed despite all other cardinal or supportive clinical features [4] [34]. A case is definitively identified as sJIA if the patient develops arthritis and fever along with other features [4] [34].

- **Systemic Features**

Fever. Fever affects virtually all patients with sJIA and is the most common symptom [10]. The fever typically spikes daily and is therefore described as quotidian or double quotidian, defined as having one or two spikes of a temperature exceeding 39°C, in a given day, followed by drops in temperature to normal levels or even below baseline [10]. A child with sJIA is usually unwell and exhausted, and rashes become more pronounced during fever episodes. In accordance with the definition, the fever must last for at least 2 weeks to justify a diagnosis of sJIA. In a Pennsylvania cohort, 51% of patients had a fever attributed to sJIA but did not meet the ILAR criteria for a typical fever [10]. In the CARRA

Table 2. Proposed definition of systemic juvenile idiopathic arthritis; First Step, 2019. Adapted from Martini, A., Ravelli, A., Avcin, T., Beresford, M.W., Burgos-Vargas, R., Cuttica, R., *et al.* (2019) Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. *Journal of Rheumatology*, **46**, 190-197.

<i>Daily fever documented for at least 3 consecutive days with quotidian pattern reoccurring over at least 2 weeks with 2 major criteria or one major criterion and 2 minor criteria</i>	
Major Criteria	Minor Criteria
<ul style="list-style-type: none"> • Evanescent erythematous rash • Arthritis 	<ul style="list-style-type: none"> • Generalized lymph node enlargement and/or hepatomegaly and/or splenomegaly • Serositis • Arthralgia lasting for 2 weeks or longer (in the absence of arthritis) • Leukocytosis (equal or more than 15,000/mm³) with neutrophilia

cohort, only 25% of patients had a fever that met the baseline requirements for quotidian fever [16]. It is important to note that fevers that do not drop back to baseline or below might be a sign of severe infection or sJIA-complicated MAS [35].

Lymphatic and reticuloendothelial organ involvement: Another important feature is lymphadenopathy, which occurs in one-tenth to one-fourth of patients and is characterized by being generalized, non-tender, variable in size and with reactive hyperplasia when those nodes are checked histologically [4] [10]. Hepatomegaly, splenomegaly or a combination of the two comprises another element of the classification criteria, but they present in only 8% of patients [4] [10] [16].

Serositis: Serositis is another characteristic feature of sJIA found in approximately 7% of patients [10] [16]. Pericarditis, pericardial effusion, pleuritis and pleural effusion may also occur during the disease. Most serositis cases in the context of sJIA are asymptomatic and therefore tend to be discovered radiologically, but a few patients may experience pericardial chest pain that becomes more prominent when lying supine, with pleuritic pain upon inhalation, cough and dyspnea or abdominal pain [4].

Sorethroat: Sore throat (*i.e.*, pharyngitis) is a criterion of AOSD based on the 1992 criteria by Yamaguchi and the 2002 criteria by Fautrel; it may be characteristic of sJIA presenting during adolescence but is not often reported among younger patients [4] [31].

• Dermatological Features

The most common skin feature is an evanescent (fast to self-resolving) salmon coloured maculopapular rounded or oval-shaped rash that coincides with fever episodes and disappears after the patient's temperature drops [4]. This type of skin eruption is part of the ILAR criteria for sJIA [1]. It occurs in approximately 61% to 80% of patients and is commonly found on the trunk, upper thighs and arms or neck [10] [16]. A biopsy of this characteristic rash showed lymphocyt-

ic-predominate, neutrophilic or mixed infiltrate, along with remarkable expression of endothelial and epithelial markers [36] [37]. The kobener phenomena can be elicited in sJIA, but this is not pathognomonic because it can also occur in other diseases [4]. Pruritic urticaria and pustular rash are also occasionally described but are less common in sJIA [4].

- **Arthropathy Features**

According to the ILAR's 2001 criteria, the presence of arthritis is one prerequisite for a diagnosis of sJIA. Arthritis can occur at the initial presentation, within the first 3 months or even later [10]. Joints subject to involvement in sJIA include wrists, knees, hip joints, ankles, the temporomandibular joint and cervical joints [4] [38] [39] [40]. Arthritis can be polyarticular, oligoarticular or, less frequently, monoarticular. In addition, it can persist for 2 years in more than one-third of patients [10] [16]. This is quite alarming because it can cause the destruction of joint structures, evidenced by erosion, narrow joint spaces and ankylosing [41]. Such destructive arthropathy may lead to serious limitations of joint movement and function, affect limb growth, require early joint replacement and even lead to micrognathia and cervical spine deformity, especially with delayed recognition of the disease [4]. Arthralgia may occur at the disease's onset but is still not included as part of the ILAR classification criteria for sJIA [16] [31]. In contrast, in the AOSD criteria, arthritis is not a necessary sign for diagnosis [38]. It is important to note that MAS may complicate sJIA at the time of presentation and that a lack of arthritis is found more frequently in sJIA cases with concomitant MAS than active sJIA alone [42].

- **Other Atypical Manifestations of Systemic Juvenile Idiopathic Arthritis**

Interstitial lung diseases are reported rarely [43] [44]. Patients may present with cough, hypoxia and clubbing, which are associated with a high frequency of IL-6 inhibitor reactions [43] [44]. Alveolar proteinosis and endogenous lipoid pneumonia are the most common pathological findings upon lung biopsy [43] [44]. Radiologically, the patterns found include diffuse ground-glass opacities, subpleural reticulation, interlobular septal thickening and lymphadenopathy [43] [44]. Pulmonary hypertension has also been rarely documented [4].

Some children may present with Kawasaki disease (KD) manifestations with or without coronary artery aneurysm, and these cases tend to be unresponsive to typical management with intravenous immunoglobulin and aspirin [45] [46]. In a U.S. database study of more than 6000 KD cases, 0.2% were presumed to have KD and then diagnosed with sJIA. MAS is more associated with sJIA cases than KD cases (30% with sJIA with KD versus 0.3% with KD only) [46]. The frequency of coronary artery abnormalities was not statistically different between the cases that turned out to be sJIA with KD versus KD-only cases [46]. Intracardiac mass and valvulitis have been rarely reported with sJIA [47].

Aseptic meningitis and uveitis have been infrequently documented with sJIA [4]. Proteinuria and secondary amyloidosis have been described in AOSD, but rarely in sJIA in the literature, and may benefit from biologic treatment [48] [49]. Renal amyloidosis complications appear more frequently in patients with

sJIA who carry familial Mediterranean fever gene mutations [50].

- **Macrophage Activation Syndrome**

MAS is a secondary form of hemophagocytic lymphohistocytosis (HLH) syndrome associated with autoimmune and autoinflammatory diseases, classically with sJIA, that leads to bone marrow failure and pancytopenia [51] [52]. As its name suggests, it results from the engulfment of blood cells by activated macrophages (histiocytes) and persistent T lymphocytes and macrophage activation in the reticuloendothelial organs, leading to cytokine overproduction [53] [54]. In animal models, MAS can be induced by repeated toll-like receptor-9 (TLR-9) stimulation in mice with normal genetic makeups [55]. Clinical manifestations include high fever, being unwell and splenomegaly, as well as signs of bone marrow failure such as petechiae, bruises and pallor [51] [52]. Extreme hyperferritinemia is a significant finding in 95% of cases [56]. Hypertriglyceridemia, low serum fibrinogen and declining erythrocyte sedimentation rate (ESR) are distinguishing laboratory features of MAS [51] [52].

Classification criteria were developed to assist physicians in detecting MAS in patients with sJIA in 2016; they suggest that MAS should be diagnosed when a child with a confirmed or presumptive diagnosis of sJIA is febrile and has hyperferritinemia (more than 684 ng/ml), as well as two of the following four abnormalities: low platelets (less than or equal to $181 \times 10^9/L$), high aspartate aminotransferase level (AST); (greater than 48 units/L), high triglycerides (more than 156 mg/dl) or low fibrinogen (less than or equal to 360 mg/dl) [57]. These 2016 MAS classification criteria, although they are not considered diagnostic, appear to detect more cases of MAS, appear to be more sensitive and more inclusive and have a lower threshold to diagnose MAS in sJIA than the previously used metrics, such as the primary HLH 2004 criteria [57] [58]. A retrospective study that compared the available classifications found that MAS that complicated sJIA was not diagnosed at all when using HLH-2004 criteria, but the 2016 classification criteria detected MAS in 11% of patients [59].

A recent study reported that a high ferritin-to-ESR ratio can be used to differentiate sJIA complicated by MAS from only an active phase of sJIA, with acceptable sensitivity and specificity of 82% and 78%, respectively [56]. Recently, MAS/sJIA (MS) scoring, another diagnostic scoring system used to differentiate sJIA complicated by MAS, was introduced in 2019 and validated with a sensitivity of 85% and a specificity of 95% [42] [60]. The MS scoring system is based on the following components: presence of central nervous system manifestation, presences of hemorrhagic manifestation, lack of active arthritis, level of platelets, fibrinogen, ferritin and lactate dehydrogenase (LDH) [42].

MAS can occur at the onset of the disease or during its course even if the patient is receiving treatment [35] [61]. The prevalence of MAS in patients who had bone marrow aspirate and a diagnosis of sJIA was around 13% in a retrospective cohort [62]. Moreover, there is an increased awareness that MAS may occur in subclinical or partial form in almost one-third of patients with sJIA, which explains the low laboratory threshold for 2016 MAS classification criteria

[63]. The concern has also been raised that biologics might mask MAS; patients with sJIA who were treated with canakinumab and tocilizumab tended to develop MAS with lower ferritin levels than the historical cohort. In addition, tocilizumab-treated patients tended to be less febrile, but with lower levels of platelets and fibrinogen and higher AST levels [61].

7. Laboratory Findings

At present, no single test can confirm a sJIA diagnosis. Increased acute phase reactant is a hallmark, as are leukocytosis, thrombocytosis, increased ESR and C-reactive protein (CRP) level in around 85% - 95% of cases [4] [64]. Anaemia is another common finding [4] [64]. Moreover, elevated ferritin above 500 ng/ml occurs in approximately 70% of cases, and increased AST or alanine aminotransaminases (ALT) occurs in one-fourth of cases [64]. Extremely high ferritin in the presence of low ESR increases the possibility of MAS [56]. Extremely high platelet levels (above 1000×10^9 /litre) should increase the suspicion of KD [46]. Antinuclear antibodies (ANA) and the rheumatoid factor are typically negative in sJIA [4].

Other laboratory tests that might detect complications or exclude other mimickers include the following: microbiological cultures and viral panels, peripheral blood smears, bone marrow aspiration, biochemical panel for MAS (LFT, Triglycerides, LDH and coagulation profile including fibrinogen and D-dimer), genetic studies, echocardiography and chest X-ray [4] [64]. Phagocyte-specific protein S100, if available, is a good biomarker to differentiate sJIA from other febrile illnesses [34] [65]. Procalcitonin is an acute phase reactant, and data are not adequate to determine its role in sJIA [34].

8. Differential Diagnoses of sJIA

The diagnosis of sJIA is largely clinical, so it is necessary to proceed by first excluding other serious systemic illnesses, such as infection and malignancy, before commencing the mainstay treatment [64]. Malignancies, especially leukaemia and lymphoma, can mimic sJIA and its concomitant MAS [64]. A careful review of symptoms, peripheral blood smears and even bone marrow aspirate or lymph node samples as indicated on a case-by-case basis, are extremely helpful when seeking to exclude malignancy. Infections that may cause viral exanthema, such as measles, parvovirus, influenza, parainfluenza, herpes virus 6, Epstein-Barr virus and cytomegalovirus, must be ruled out [4] [64]. Viral exanthem tends to be persistent and not fleeting like the evanescent-rash associated with sJIA [4] [64]. Differential diagnoses of arthritis, such as septic arthritis, post-infectious arthritis, rheumatic fever, transient synovitis, Lyme disease and brucellosis, should be entertained when a child presents with fever and arthritis, as indicated by the case [64]. Other autoimmune and inflammatory conditions that may mimic sJIA to a great extent include systemic lupus erythematosus (SLE), KD and other vasculitic diseases, periodic fever syndromes and even other causes of HLH (familial or acquired) or immunodeficiencies [64] [66] (see **Table 3**).

Table 3. Mimickers of systemic juvenile idiopathic arthritis.

Mimickers of systemic juvenile arthritis (and vice versa)	Examples
Infection	<ul style="list-style-type: none"> • Deep-seated infections: abscesses or osteomyelitis • Prolonged fever causes: tuberculosis, brucellosis • Post-infectious arthritis: streptococci • Viruses: EBV, CMV, parvovirus, measles, HIV
Malignancy	Leukemia or lymphoma
Autoimmune disease	SLE or polyarticular JIA with systemic manifestations
Vasculitis	KD or polyarteritis nodosa
Autoinflammatory periodic fever diseases	TNF receptor periodic fever
Immunodeficiencies	Especially those that may present with HLH

9. Treatment Outline of Systemic Juvenile Idiopathic Arthritis

The aims of treatment are suppression of the inflammatory process; prevention of joint damage; controlling articular and systemic symptoms; optimizing function; supporting the growth, motor and social development of affected children; and minimizing medication toxicity and side effects [6]. Treating to target is an approach that is well supported by paediatric rheumatology guidelines and defined by reaching clinical remission or low disease activity at minimum [6]. The treatment should be individualized to the patient's and the disease's characteristics and agreed upon by the child and parents. Evaluating the severity including the persistence of systemic manifestations, degree of joint involvement, critical organ involvement, history of relapses, response to treatment and presence of MAS is a crucial part of providing the most suitable targeted treatment regimen [6].

The immediate goal of treatment is to quickly decrease the fever within a week, as well as alleviate serious complications, such as active pericarditis and pleuritis and severe MAS, to control other articular and non-articular manifestations during the first 3 months of the disease, with a minimum improvement of 50% from the start of the therapy [6] [34] [67]. Clinical disease inactivity or low disease activity should be reached by 6 months [6] [34] [67]. A tighter time frame is needed in the management of sJIA in comparison to other subtypes of JIA because of the serious complications of systemic manifestations, such as MAS, and evidence of earlier inflammatory control will lead to better prognosis [6].

Although corticosteroids have been considered a mainstay treatment for many decades, anakinra was also proven effective and relatively safe as initial monotherapy in longitudinal observational studies [5] [34] [68]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate are still in use, particularly to control mild symptoms initially and to manage arthritic manifestations, respectively, given their well-known safety profiles and cost [34] [68].

- **Corticosteroids**

Corticosteroids are considered the mainstay in the management of moderate-to-severe symptoms of sJIA [69]. If a patient is severely affected, intravenous pulse therapy with methylprednisolone (30 mg/kg/day for 1 - 3 days) should be initiated [68]. Oral corticosteroids can be started using prednisolone or prednisone at doses of 1 mg/kg/day up to 2 mg/kg/day and then reassessed weekly or monthly depending on the response and disease activity [68]. All efforts should be made to decrease the dose and duration of corticosteroids to minimize long-term toxicity by tapering the oral corticosteroids to 0.5 mg/kg/day and then weaning off of it as soon as remission or low disease activity is reached [68]. If clinical status worsens or is unchanged, despite optimization of the oral corticosteroids to a 2-mg/kg/dose in the initial few weeks, additional therapy with biologics should be added [68].

- **Biological DMARDs**

Many experts believe that earlier modulation and suppression of cytokine release might potentially decrease the long-term impact of the disease, signifying the notion that a “window of opportunity” exists and leading to the successful management of such a disease [70]. Therefore, treatment is recommended as early as possible to achieve early control of inflammation and cytokine storm and subsequently avoidance of chronic arthritis [6]. It is also well known that a persistently active disease that involves persistent fever and requires corticosteroids for more than 6 months has a poor functional outcome [71] [72].

- 1) **IL1 Inhibitors:**

Since Pascual's 2005 report on IL-1's role in the pathogenesis of systemic JIA and its clinical effect, the usage of IL-1 inhibitors has increased [73] [74] [75]. Anakinra and canakinumab are the most-used medications from this category and have received approval from most drug authorities around the world [7]. Riloncept is an investigational drug [7] (see **Table 4**).

Using Anakinra: In 2011, a double-blinded randomized control study called the ANAJIS trial was published regarding the efficacy of daily subcutaneous (SC) anakinra in 12 sJIA patients allocated to each arm with persistently active disease despite corticosteroid use [21]. The study proved the short-term efficacy and safety of anakinra, with almost 92%, 58% and 42% of patients who received anakinra showing statistically significant resolution of fever and improvement of arthritis using the JIA-American College of Rheumatology Pediatric's 30 response criteria (ACRpedia 30), ACRpedia 50 and ACRpedia 70, respectively, compared to 58%, 0% and 0% of participants in the placebo group [21]. Ter Haar prospectively studied 42 patients with newly diagnosed sJIA who were treated with anakinra first as monotherapy and she followed them up for 5 years; three-quarters of the cohort showed inactive disease at the 1-year mark, whereas almost all showed inactive disease at 5 years [5]. One-third of the cohort needed corticosteroids during the treatment [5]. Furthermore, excellent clinical response to anakinra at 1 year was more noticed in patients with the following

Table 4. A summary of currently used biologics for systemic JIA.

Drug and studies included in this summary	Mode of action	Effectiveness as per studies included in this summary	Dosage and route
Tocilizumab (TCZ) [22] [78]	Human recombinant monoclonal anti-IL-6 receptor	<p>An RTC study recruited sJIA patients who had uncontrolled JIA despite NSAIDs and corticosteroids usage; and received TCZ versus a placebo</p> <ul style="list-style-type: none"> By 3 months, 85% of sJIA patients who received TCZ reached ACR30 response and no fever, 71% reached ACR70 response and 37% reached ACR90 response compared to less than 25% who become afebrile and has ACR 30 in the placebo group [22] Three-quarters of patients with sJIA treated with TCZ had higher height velocities (6.6 cm/year) [78] 	<ul style="list-style-type: none"> Intravenous route Weight < 30 kg: 12 mg/kg/dose Weight > 30 kg: 8 mg/kg/dose Should be given every 2 weeks
Anakinra (ANK) [2] [5] [21]	Human recombinant anti-IL-1 receptor	<p>1) RTC study was done on sJIA patients who had persistently active disease despite CS or NSAIDs [21]</p> <ul style="list-style-type: none"> By one month, 92% of patients receiving ANK reached ACR30 response and no fever, 58% reached ACR50 response and 42% reached ACR 70 response [21] Median time to achieve remission was 33 days 76% of patients of ANK users had inactive disease at 1 year and 52% of ANK users had inactive disease while on medication [5] <p>2) A prospective cohort studied newly diagnosed sJIA patients who treated with ANK as initial treatment [5]:</p> <ul style="list-style-type: none"> At five-year-mark, 96% of patients had inactive disease and 76% of patients had inactive disease and not receiving medication [5] 	<ul style="list-style-type: none"> Subcutaneous route 2 mg/kg/day Range: 1-4 mg/kg/day
Canakinumab (CAN) [76] [77]	Monoclonal anti-IL-1 Beta	<p>An RTC included sJIA patients with active disease, could be in low dose daily CS or NSAIDs, included 190 patients:</p> <ul style="list-style-type: none"> At 15 days, 84% of CAN receivers reached ACR30 response At the open-label part, 1/3 attained inactive disease, and 73% reached ACR 50 response In the withdrawal phase, relative risk reduction of flares was 64% lower in the CAN group 33% of patients received CAN discontinued CS 	<ul style="list-style-type: none"> Subcutaneous route 4 mg/kg/dose Max dose: 300 mg Should be given every 4 weeks
Rilonacept [84] [85] Did not receive JIA approval Investigational	complex protein consisting of three fused parts Acts against IL-1 alpha and IL-1 beta	<ul style="list-style-type: none"> At 4 weeks, 60% and 40% of the rilonacept-treated group had ACR50 response and ACR70 response, versus 30% and 12% of those in the placebo group respectively. Time to respond was shorter in the rilonacept-treated group The CS has been weaned off in most of patients who received rilonacept. 	<ul style="list-style-type: none"> Subcutaneous Should be given weekly 4.4 mg/kg loading dose and then 2.2 mg/kg weekly doses

Abbreviations used in **Table 4**: ANK: anakinra, CAN: canakinumab, CS: corticosteroid, TCZ: tocilizumab.

clinical profile: shorter disease duration, presence of a higher degree of systemic manifestations, higher ferritin and neutrophil count and lower active joints at the start and early complete response to anakinra at 1 month [72] [73] [74]. On the basis of the growing evidence on anakinra's effectiveness and safety profile, the relative ease of administration and the feasibility of using the medication at home, anakinra has become the first option to treat sJIA, when it is affordable, to avoid corticosteroids and their long-term complications and to achieve early induction of remission [2] [5] [70].

Many studies showed that a longer duration from the onset to diagnosis and treatment with biologics tends to lead to poorer treatment response [72]. In a retrospective study, the only difference between responders to anakinra and non-responders was the time between the onset of disease and the start of anakinra treatment, with a mean of around 2 months in the responder groups versus a delay of 2 years from the start anakinra in the non-responder groups [73].

Side effects of anakinra include post-injection pain and injection site erythema, thrombocytopenia, infections including laryngitis, bronchitis, atypical pneumonia, varicella, herpes simplex, cutaneous infection, gastroenteritis and UTI [2] [5] [21]. Refer to **Table 5** for a review of side effects of common medications have been used to treat sJIA.

Using Canakinumab: Canakinumab is a selective human anti-interleukin-1 β monoclonal antibody. Canakinumab has shown efficacy in treatment of active sJIA, with a significant portion of patients reducing their steroid use. The effect is fairly sustainable, but medication cessation is common [76] [77]. A double-blinded phase of the randomized clinical trial led by Ruperto showed that 81%, 79% and 67% of patients in the canakinumab arm achieved adapted ACR30, adapted ACR50 and adapted ACR70, respectively, at the 1-month mark, versus 10%, 5% and 2% of patients in the placebo group [76]. A longitudinal study showed that half of patients unfortunately discontinued medication, principally due to inefficacy [77].

Forty out of 100 patients per year reported side effects, including flare of sJIA, MAS and infections [61] [76] [77]. Increased LFT was occasionally reported (0.63 out of 100 patients per year) [76] [77]. Refer to **Table 5** for a review of side effects of common medications have been used to treat sJIA.

2) IL-6 Inhibitors and Use of Tocilizumab (TCZ):

TCZ is an anti-interleukin-6 receptor antibody. It is proven to be effective in treating active sJIA uncontrolled with first-line corticosteroids or anakinra. A randomized control study with a 12-week double-blinded phase recruited 112 sJIA patients who had uncontrolled JIA despite NSAID and corticosteroid usage, and they received TCZ or a placebo [22]. By 3 months, 90% and 85% of sJIA patients had reached an ACR30 and ACR50 response and had no fever, compared to only 24% and 10% of patients in the placebo group [22]. Fever and rash and laboratory abnormalities (anaemia, thrombocytosis and hyperferritinemia) also significantly decreased in the TCZ group. In the open-label phase at 52 weeks,

Table 5. Medication side effects.

Medications	Side effects	Recommended monitoring
NSAIDs [84]	GI upset Gastritis Hepatotoxicity Nephrotoxicity	Symptoms check Periodic LFT and RFT
Corticosteroids [69]	Pulse doses <ul style="list-style-type: none"> • Hypertension • Hyperglycemia • Behavioral changes Chronic use <ul style="list-style-type: none"> • Diabetes • Hypertension • Osteopenia • Obesity • Skin: stria and acne • Eyes: cataract and glaucoma • Hypothalamic pituitary adrenal axis dysfunction 	<ul style="list-style-type: none"> • Periodic fasting serum glucose test • Regular blood pressure measurement with each visit • Annual lateral lumbar spine X-rays and DEXA scan if patient continues on CS more than one year • Yearly eye exam by ophthalmologist for slit lamp examination and intraocular pressure measurement
Conventional DMARDs <ul style="list-style-type: none"> • MTX [85] [111] • Cyclosporine [87] [88] 	MTX <ul style="list-style-type: none"> • GI symptoms and gastritis • Mucocutaneous manifestations such as rash, mouth ulcers or alopecia • Elevated transaminases • Pneumonitis • Leucopenia and thrombocytopenia • Infection Cyclosporine <ul style="list-style-type: none"> • Nephrotoxicity • Hypertension • GI symptoms: nausea, vomiting, diarrhea • Elevated transaminases • Headaches, tremor, seizure • Gingival hyperplasia • Hypertrichosis • High lipid profile 	MTX <ul style="list-style-type: none"> • Baseline and periodic CBC, ESR, LFT, RFT, urinalysis • Live vaccines are contraindicated • Baseline varicella titres and MMR before treatment Cyclosporine <ul style="list-style-type: none"> • Baseline and periodic creatinine, urea and electrolytes tests • Lipid profile • Monitor blood pressure
IL-1 inhibitors (anakinra and canakinumab) [2] [5] [21] [76] [77]	<ul style="list-style-type: none"> • Hypersensitivity reaction and can cause serious anaphylaxis • Flare up of a LTBI • Infections (herpes zoster, salmonella, coccidioides) • Increase liver enzymes • Thrombocytopenia 	Periodic CBC, LFT, RFT and coagulation profile
Tocilizumab [22] [78] [79] [80]	<ul style="list-style-type: none"> • Infections such as URTI and herpes reactivation • Neutropenia (0.77 incident/patient-year) • Hepatic toxicity (3.33 incident/patient-year) 	Periodic CBC, LFT, RFT and coagulation profile

59% of participants had reached ACR90 and fever resolution, 48% had reached no active joints and 52% had discontinued corticosteroids [22].

The longitudinal open-label study following up with the above cohort showed the catch-up growth of children who used TCZ. At least three-quarters of patients with sJIA treated with TCZ had greater height velocities (6.6 cm/year) [78]. There is no head-to-head comparison between anakinra and TCZ.

An earlier 6-week open-label study in 2008 also showed the more impressive efficacy of TCZ in children with sJIA, with 90% reaching ACR pedia 30 and 86% reaching ACR Pedi 50 [79]. The second part of the study was a double-blinded randomized placebo-controlled study conducted for 12 weeks until withdrawal for rescue, with an open-label extension phase lasting 48 weeks. The results at 48 weeks were remarkable, with more than 90% reaching ACR pedi 70 [79].

TCZ has been approved for children older than 2 years [80]. A Phase 1 trial for children younger than 2 years was recently published and indicated that the pharmacokinetics and pharmacodynamics of the drug were comparable with those of the older group (>2 years), but the trial pointed to a higher frequency of serious hypersensitivity in the younger group (27% versus 2.6%) [80].

Neutropenia of grade 3 and above appeared to occur in 25% of cases. Infections such as varicella, herpes, lower airway infections and gastroenteritis are documented during TCZ treatment and do not appear in association with neutropenia [22] [81]. Increased ALT and AST levels are also a frequent side effect [22]. Severe hypersensitivity and MAS are reported and might cause withdrawal from treatment [22] [43] [61]. Refer to **Table 5** for a review of side effects of common medications has been used to treat sJIA.

Examples of investigational IL-6 inhibitors that have been used are IV siltuximab and sarilumab for refractory sJIA [82]. An ongoing clinical trial examined the pharmacokinetics of sarilumab, an IL-6 receptor monoclonal antibody [83].

Other Modalities of Treatment:

- **Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

NSAIDs are initiated early in the course for newly diagnosed sJIA, continue until diagnostic investigation is complete and may alleviate mild arthralgia and arthritis. An NSAID trial could be useful for cases characterized by the absence of severe systemic symptoms and no signs of MAS, according to a 14-year retrospective chart review study in an Italian tertiary hospital that showed that one-fourth of patients reached the status of disease inactivity in around 7 weeks (median) while they were on NSAIDs monotherapy [84]. Those patients who were responsive to NSAIDs monotherapy were younger at the time of the presentation and had lower joint counts and lower initial CRP levels in the above-mentioned study [84].

Ibuprofen, naproxen or indomethacin can be used. If symptoms and inflammation are not under control or proceed to escalate, upgrading treatment to include steroids or biologics is warranted.

- **Conventional DMARDs**

Methotrexate used to be most commonly utilized as a steroid-sparing medi-

cations for patients with severe symptoms and early MAS [85]. However, its use has been declining because of its limited effectiveness [85]. It is still considered effective for persistent articular symptoms in combination with steroid or biologic line therapy [34] [68]. A methotrexate-only regimen is unlikely to lead to clinical remission and is inappropriate therapy for the hyperinflammatory phase [86].

Cyclosporine is another agent indicated for refractory or chronically active sJIA [9] [87]. A recent observational study showed that cyclosporine led to favourable outcomes in 75% of refractory steroid-dependent sJIA cases in areas where the availability of biologics was limited and too expensive to cover the cost [88].

Other Medication under Investigation:

- Jak inhibitors usage has increased lately in cases with evident inflammation [89]. A few case reports have shown positive results for patients with refractory sJIA [90] [91]. A clinical trial investigating the efficacy and safety of tofacitinib is ongoing [92].
- Tacrolimus was studied retrospectively in a small cohort study of six Chinese children with sJIA. Results showed that tacrolimus use led to a decrease of corticosteroid use at 6 months and 12 months [93]. IL-6 expression reduction was postulated as the tacrolimus mechanism of action to treat sJIA [93]. No randomized controlled trial has studied the efficacy of tacrolimus in sJIA.

10. Common Questions in the Management of sJIA

Among biologic and non-biologic treatment options, which treatment should preferably be started first for a patient suspected to have sJIA?

Based on the available guidelines, the initial treatment for patients with systemic features with or without arthritis should be either a high-dose steroid (whether an IV pulse steroid or oral prednisolone at 1.5 - 2 mg/kg/day with a tapering schedule) or anakinra monotherapy. The aim after starting medication in the first week is fever resolution and reduction of CRP by 50% [6] [34] [68]. Daily to weekly assessment is crucial in the first month until disappearance of inflammation. TCZ or canakinumab has not yet been recommended for use as an initial monotherapy as per the latest guidelines, due to the lack of studies in this scope [34]. In contrast, a CARRA case-based survey in 2013 pointed out that some paediatric rheumatologists may opt to use TCZ as one of the initial treatment plans in the first 9 months with or without steroids [68].

What is the next management step if there is evidence of an inadequate response to the initial treatment regimen, such as corticosteroids or anakinra?

If an inadequate response is confronted, repeating the pulse steroids, increasing the dose of steroids or anakinra or adding steroids or anakinra to the initial regimen is highly recommended to attain better disease control [34]. If the patient develops recurrent flares, persistent systemic manifestations or dependency

on steroids, then it is advisable to add IL-6 or IL-1 inhibitors, if the patient is exclusively treated with steroids, or to increase or change of the biologics, if the patient is already on one of the biologics [34].

Physicians should frequently assess the disease activity and ideally aim to reach clinically inactive disease [6]. The definition of inactive disease typically involves resolution of systemic manifestations (fever and rash), arthritis and laboratory abnormalities such as high CRP level, anaemia, thrombocytosis, hyperferritinemia and any other complications (e.g., MAS) [94] [95].

How should sJIA with predominant arthritis treated?

Based on ACR guidelines, initial treatment for those with predominant arthritis varies between usage of NSAIDs for 1 - 2 months, of intraarticular steroids if patients have very few joints involved or even of add-on methotrexate or leflunomide if there is a higher number of joint counts [96]. In the case of failure of these treatments or inadequate response, anakinra is recommended [96]. In the case of no response, abatacept or TCZ is recommended [96].

The latest German guideline suggests starting with a glucocorticoid and utilizing biologics such as anakinra [34]. If the response to anakinra is inadequate, TCZ or canakinumab is recommended [34]. At 4 weeks' time, arthritis is expected to resolve by at least 50% as an indicator of treatment success [34]. Third-line treatment with TNF inhibitors such as etanercept or adalimumab, abatacept or MTX can be added if first- and second-line treatment has failed to control the arthritis-predominant sJIA [34]. Intraarticular glucocorticoids may be used [34].

What is the role of combining different biologics?

Combination of biologics is discouraged [34]. If a biologic treatment proves unsuccessful or leads to serious adverse effects, the physician should stop the treatment and start using the another biologic, with no washout period needed [34].

How should one follow-up on patients with sJIA who are on medication?

Assessment and management of patients with sJIA might involve hospitalization, either to confirm the diagnosis and exclude other serious mimickers or until systemic manifestations (especially fever), critical severe organ involvement (pericarditis, or lung involvement, etc.) or MAS have lessened [9]. Weekly assessment might be suitable for active sJIA with high disease activity, and then assessments monthly to every three months for moderate to low disease activity to adjust medication accordingly (see **Figure 1**).

The targets of treatment are the following:

- Within one week of treatment commencement, fever resolution and 50% reduction of CRP level are expected [6] [34].
- Four weeks after the start of treatment, 50% improvement of disease activity is expected, such that there will be either a JADAS-10 score of 5.4 at maximum or at least 50% improvement and reduction of the following measures: physician global disease activity or active inflamed joint counts [34].

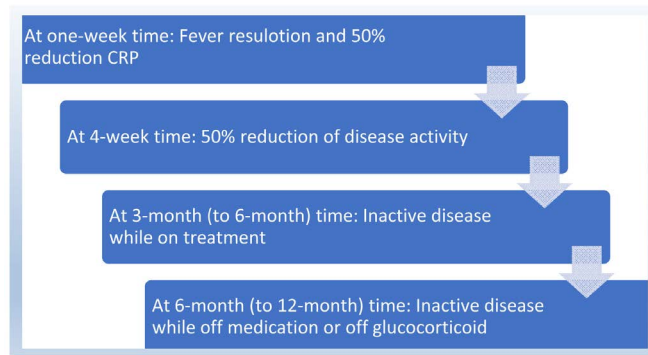


Figure 1. Treatment goals for systemic juvenile idiopathic arthritis in stepwise fashion. Figure is adapted from: Hinze, C.H., Holzinger, D., Lainka, E., Haas, J.P., Speth, F., Kallinich, T., *et al.* (2018) Practice and Consensus-Based Strategies in Diagnosing and Managing Systemic Juvenile Idiopathic Arthritis in Germany. *Pediatric Rheumatology*, 16.

- Clinically inactive disease or low disease activity should be reached while the patient is on treatment at 3 - 6 months after commencing it [6] [34].
- The best clinical outcome would be clinical remission is reached within 6 months or 12 months at maximum while the patient is on no glucocorticoids, on or off other medication.

Disease activity has been quantified by different measures for research purposes to ensure objectivity. Examples of these scales are the juvenile idiopathic arthritis JADAS-10, the modified systemic JADAS score or the physician global score. The JADAS-10 score includes: 1) the physician global assessment (range 0 - 10), 2) the patient's or parent's global assessment (range 0 - 10), 3) the active joint count (range 0 - 10) and 4) the normalized erythrocyte sedimentation rate after 1 h (score = [observed rate - 20]/100) or C-reactive protein level (score = CRP in mg/l - 10]/100) [97].

Disease inactivity is defined as per modified Wallace criteria as the absence of active arthritis, morning stiffness and systemic features (fever/rash/serositis/splenomegaly/lymphadenopathy due to JIA); a physician global assessment that indicates no disease activity (<10 on a scale of 0 - 100); and normalization of ESR (<20 mm/hour) and CRP levels (<10 mg/litre) [94] [95].

When should the patient be weaned off of medication?

Within the first 3 to 6 months, the aim is to reach inactive disease to plan the weaning off of medication to achieve clinical remission [34]. A recent survey was conducted and showed that most rheumatologist participants would agree with Wallace criteria as the matrix to define clinically inactive disease in sJIA. Tapering medications should be decided on the basis of patients reaching clinical remission on medication (CRM), defined as 3 to 6 consecutive months or more of inactive disease while on medication [98]. However, a few rheumatologists understandably would like a more stringent approach, with 1 year of clinical remission while patients are on medication [98]. It is advisable to taper steroids early and first because of their side effects within the first 6 months, even before patients reach full CRM [34] [98].

How should patients be weaned off the medications used to treat sJIA?

- Steroids should be tapered gradually from a high dose to lower doses very early, within 1 - 3 weeks, if systemic inflammatory symptoms have subsided [98]. Then, weaning off of a steroid gradually should be planned within the first 6 months [34].
- Past failure to taper, intolerance or toxicity of medications, previous flares and MAS were important factors in surveyed rheumatologists' decisions on when to taper medications [98].
- Weaning patients off of anakinra is usually accomplished by using an alternate-day regimen, which means using it every other day for a month and then stopping its use if the child continues to be in remission clinically and biochemically [5] [21]. The length of the withdrawal period varies substantially, from a month to more than 6 months [98].
- TCZ and canakinumab are usually tapered by lengthening the interval between the doses over period of 2 - 6 months or longer, rather than by decreasing the dose [22] [77] [98].
- Closer follow-up with clinical and laboratory reassessment is needed after medication withdrawal [34] [98].

11. Prognosis and Fatality

The mortality due to sJIA is reported and related to the following causes: MAS, infection, treatment-related complications and disease-related complications (such as pulmonary interstitial lung disease, alveolar proteinosis, myocarditis, etc.) or malignancy [99] [100] [101].

The data in the pre-biologic era showed that the standardized mortality rate of systemic JIA reached a level of 1.8/1000, based on an American registry [99]. In the modern era, the mortality rate and standardized mortality rate of sJIA have been higher than those of non-systemic JIA. In 2014, it was reported that the mortality rate due to sJIA reached 3.9/1000 person-years, and the standardized mortality rate reached 8 per 1000 of the population, based on a UK cohort [100]. There were five deaths out of 196 sJIA cases in a later cohort, and the reported causes of death were infection, complication of stem transplant, MAS, asthma and accidental overdose [100]. MAS alone complicates 10% to 36% of sJIA cases, and mortality due to MAS might reach up to 20% [51] [101] [102] [103] [104]. Occurrence of lung disease with sJIA is quite rare, but having sJIA with lung disease leads to a mortality of almost 159/1000 person-years [44].

The disease has three well-described patterns in longitudinal cohort studies, especially true for the pre-biologic era: 1) the persistent disease course (51%), defined as ongoing systemic features and/or arthritis, which leads to a higher proportion of patients with functional disabilities compared to the proportion of monophasic patients; 2) the monophasic course (42.2%), defined as one episode of systemic features and arthritis, which may last for a maximum of 24 months but are followed by complete recovery, cessation of medication and no recurrence; and 3) the polyphasic course, comprising 6.7% of patients and defined as

episodes of active systemic features and arthritis with remission periods in between them [105].

The most recent studies have shown a positive outcome of sJIA, even better than that of other forms of JIA. The short-term outcomes were investigated in an Australian inception JIA cohort study that targeted the first year of diagnosis, using a joint count of zero as an indicator of inactive disease [106]. At the one-year mark from the diagnosis, this study showed that 30% of sJIA patients had inactive arthritis with no medication, 40% had inactive arthritis while on medication and 30% had active arthritis while not on medication [106]. In another study in Turkey, almost 48% of patients reached remission while off medication [101]. In a longitudinal follow-up study based on a Nordic population of patients with JIA, the outcome was described as favourable for sJIA, with 53.8% of sJIA patients achieving remission while off medication, 8% having remission while on medication and 22% having active disease 18 years after disease onset [107]. In a very recent Canadian-based study (ReCCH-OUT), 71% of patients with sJIA achieved remission with no medication, the highest favourable result out of all JIA patients [108].

12. Comprehensive Care and Disease's Complications

There are other important issues that should be considered in parallel with medication usage to optimize sJIA care, such as the following:

- 1) Immunization record review and completion
- 2) Clearance from and further risk reduction of infections
- 3) Monitoring of growth, development and childhood well-being

1) Immunization Record Review and Completion

Immunization records should be checked and completed for each sJIA patient. If possible, all vaccines should be completed before starting an immunosuppressant because live attenuated vaccines are contraindicated in children receiving an immunosuppressant due to the risk of having a vaccine-type infection [109] [110] [111]. Moreover, these vaccines may need a few weeks to build up the expected vaccine protection and immunity, but an immunosuppressant may decrease the immune response to the vaccines. The physician should weigh the benefit against the risk of commencing corticosteroids or DMARDs before completing immunization of a child. Annual influenza vaccine administration is recommended for children and household members [112]. It is highly important to request that all household residents be completely vaccinated if there are no contraindications [109].

2) Infections and Immunosuppression Risk

Latent tuberculosis infection (LTBI) should be ruled out before the start of immunosuppressant use [6] [113]. Verifying the exposure history to a source TB case or being in high endemic areas, along with a tuberculin skin test and serum interferon gamma assay and chest x-rays, are recommended tools to determine the exposure risk and presence of the LTBI [110] [114]. Given their limitations,

the involvement of infectious disease specialists is therefore highly valuable for positive or indeterminate results of tuberculin skin test or interferon gamma assay or in cases with a history of exposure to a known open-TB case. Administration of an immunosuppressant in such cases may lead to activation of dormant TB or a disseminated disease [110] [114].

Basic instructions for patients and family members to reduce respiratory tract, waterborne and foodborne infections in the community are recommended to sJIA patients on high-dose steroids or DMARDs, especially biologics [110] [115]. These instructions include practicing hand hygiene, avoiding contact with sick individuals, reducing one's exposure to crowded confined places, drinking from a safe water supply, avoiding non-pasteurized milk, dairy products or juices, avoiding undercooked meat, seafood or eggs and limiting contact with animals [115].

Children on immunosuppressants should be seen and assessed by a physician if they develop fever or become unwell. Treatment should begin accordingly and promptly, and completion of blood count (CBC) and CRP/ESR at least should be done to rule out neutropenia and signs of MAS [4] [110]. Signs of adrenal gland inadequacy should be sought and evaluated for children with chronic use of corticosteroids [69]. Decisions related to withholding biologics and other DMARDs should be discussed with a paediatric rheumatologist to assess for the possibility of sJIA flare-ups and the patient's propensity for developing MAS [51] [57].

3) Monitoring of Growth, Development and Childhood Well-being

Chronic inflammation due to sJIA and consequently long-term usage of corticosteroids lead to a decrease of linear growth [69] [101] [116]. Since the start of the biological era, evidence has pointed to the beneficial effect of biologics on growth velocity especially tocilizumab [78], probably because of better disease and inflammation control and reduction of corticosteroid usage. Obesity or being underweight may be observed with sJIA because of chronic usage of steroids or ongoing inflammation, respectively [69] [116]. In a cohort of more than 1000 JIA patients, including 77 systemic JIA patients, there were a higher 3-year cumulative incidences, 9% for new-onset short stature and 34% for obesity [117]. Pubertal delay also is commonly encountered among patients with sJIA [118].

Children and families confronting sJIA may experience uncertainty, fear, overreaction and frustration [119] [120] [121]. Low quality-of-life scores, high pain scores, and elevated anxiety and depression scores are commonly reported in JIA [119] [120] [121]. The caring health team should communicate with patients and families to explore any emotional, social or academic difficulty caused by JIA, its complications, needed treatments and infusions and appointments.

13. Conclusion

Early identification and diagnosis of sJIA rely on consideration of it in cases with fever, articular and cutaneous symptoms and exclusion of mimicker conditions. Early recognition of sJIA and proper treatment with corticosteroids or biologics

have shown to be beneficial to control the cytokine storm associated with sJIA. Care of patients with sJIA is complex; thus, a multidisciplinary team and awareness of the disease and its complications are important to monitor the disease and long-term morbidity and mortality.

Author Contributions

AA wrote and reviewed the manuscript and prepared the figures and tables.

Ethical Approval

Not applicable.

Consent for Publication

Not applicable.

Availability of Data

Not applicable.

Conflicts of Interest

The author declares that there are no competing interests and no funding support required for this review.

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Abbreviations

sJIA: systemic juvenile idiopathic arthritis
JIA: juvenile idiopathic arthritis
ILAR: International League of Associations for Rheumatology
DMARDs: disease-modifying antirheumatic drugs
MAS: macrophage activation syndrome
MeSH: Medical Subject Headings
ACR: American College of Rheumatology
CARRA: Childhood Arthritis and Rheumatology Research Alliance
PRINTO: Pediatric Rheumatology International Trials Organizations
IL: interleukin
IFN- γ : interferon gamma
TNF: tumour necrosis factor
MHC: major histocompatibility complex
IVIG: intravenous immunoglobulins
KD: Kawasaki disease
MEFV: Mediterranean fever gene
HLH: hemophagocytic lymphohistocytosis
TLR-9: toll-like receptor 9
ESR: erythrocyte sedimentation test
LDH: lactate dehydrogenase
AST: aspartate aminotransferases
ALT: alanine aminotransferases
CRP: C-reactive protein
LFT: liver function test
CBC: complete blood count
RFT: renal function test
TCZ: tocilizumab
NSAIDs: nonsteroidal anti-inflammatory drugs
LTBI: latent tuberculosis infection
TB: tuberculosis