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Updated Overview of Juvenile Idiopathic Arthritis

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Abstract: Juvenile idiopathic arthritis (JIA) is a heterogeneous group of idiopathic inflammatory arthritis affecting children younger than 16 years of age and lasting six weeks or longer. The terminology of chronic arthritis in children has evolved from juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis (JRA) to JIA since 1995. The major criteria for the disease include disease beginning before the age of 16 and arthritis in at least one joint that lasts for more than 6 weeks after any other plausible source of joint inflammation has been ruled out.

Chronic inflammation of the joints severely restricts the patient's functional abilities and productivity in daily life. The fundamental cause of the aforementioned issues is uncontrolled inflammation. In addition to joint issues, untreated patients may suffer growth retardation, uveitis, blindness, and life-threatening MAS. Adverse pharmacological effects should also be considered (for example, osteoporosis, growth retardation caused by glucocorticoids, and so forth).Thus, JIA treatment should be quick and successful.

Keywords: Juvenile, Idiopathic, Arthritis

Introduction

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of idiopathic inflammatory arthritis affecting children younger than 16 years of age and lasting six weeks or longer. The terminology of chronic arthritis in children has evolved from juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis (JRA) to JIA since 1995. The major criteria for the disease include disease beginning before the age of 16 and arthritis in at least one joint that lasts for more than 6 weeks after any other plausible source of joint inflammation has been ruled out. (1)

Arthralgias are typical in the early stages of sJIA, however they are not always noticeable. When arthritis manifests itself, it can affect any number of joints. The most common sites of disease are the wrists, knees, and ankles. Unlike the oligoarticular and polyarticular subtypes of JIA, the hands, hips, cervical spine, and temporomandibular joints are occasionally affected. Musculo-skeletal (MSK) complaints in children with joint discomfort are common in general practise and rise dramatically after the age of ten. (2) Joint pain and soft

tissue pain are the most prevalent presentations of musculoskeletal complaints (65%), and trauma is the most common cause of all ages of children (45%). (3)

The symptoms, genetic predispositions, pathophysiology, laboratory results, illness course and prognosis of these subgroups differ. Although persistent arthritis is a common feature for all categories, extraarticular and systemic symptoms are distinguishable for each category. The Pediatric Rheumatology International Trial Organization (PRINTO) recently suggested and is formally validating a new preliminary data-driven classification for. (4)

Etiology

The exact etiology of JIA is unknown; however, it is largely believed to be caused by an immunogenic mechanism involving both hereditary and environmental factors. (1) One unique genetic linkage connected to JIA can be discovered in the HLA region. HLA-A2 is associated with early-onset disease, HLA-B27 with enthesitis-related arthritis, and other JIA subtypes are connected with particular HLA gene alleles. (5)

In a genetically susceptible individual, abnormal immune responses generated by combinations between environmental stimuli are hypothetical. Some environmental factors, such as antibiotic exposure and C-section deliveries, can be risk factors; however, breastfeeding and household siblings can be protective**.** (6) Microorganisms such as Parvovirus B19, Epstein-Barr virus (EBV), enteric bacteria, Chlamydophila pneumoniae, and streptococcal infections remain unknown. (7)

Epidemiology

JIA is the most frequent rheumatic condition observed in Western children. Depending on study design*s*, disease categories, and geographical areas, the incidence and prevalence range from 1.6 to 23 new cases per 100,000 children and 3.8 to 400 cases per 100,000 children **.** (8) According to a study conducted in the United States and Canada, the incidence of JIA ranges from 0.041 to 0.061 per 1000 children**.** (9) According to the Utah Population Database, the frequency in white populations is 1.2 per 1000. In siblings, the relative risk of JIA ranges from 15 to 30, equivalent to the relative risk of type 1 diabetes **.** (10)

Pathophysiology

JIA subtypes are a diverse set of disorders with multiple and distinct pathologies. It is unclear how the combination of environmental stimuli and genetic predisposition disrupts the balance of regulatory and effector cells in the pathogenesis of JIA. Adaptive immune system seems to play the main role in oligoarticular JIA , polyarticular JIA , ERA & early-onset PsJIA. Where as Innate immune system plays the main role in sJIA. So far, the studies have shown that the main probable mechanism involved in both oligoarticular JIA, polyarticular JIA is imbalance between inflammatory Th1/Th17 and Treg cells. (11)

HLA-B27, which is implicated in the presentation of an unidentified arthritogenic peptide, activates T cells and induces endoplasmic reticulum stress in ERA. Autoinflammatory stimulation of the synovial-entheseal complex and autoimmune processes in extra-articular tissues appear to be the primary players in PsJIA. Abnormal activation of phagocytes leads to hypersecretion of pro-inflammatory cytokines in sJIA. (11)

Serological biomarkers in JIA patient tissues can be divided into two categories: those that remain stable and persistent throughout the disease course (antibodies like RF) and those that fluctuate with time and disease activity (cytokines like IL18). Non-systemic JIA etiology involves ANA, RF, anti-cyclic citrullinated peptide (anti-CCP), and antibodies against mutant citrullinated vimentin (anti-MCV). (12)

RF is an antibody specific to the Fc region of IgG; it was first recognized as a crucial serological marker in patients with adult rheumatoid arthritis (RA) and then detected in a tiny subset of pJIA patients (only 5% of overall JIA patients). (13) RF positive is related with a bad prognosis of JIA and the rapid production of bone erosions. (14) Anti-CCP activates complement and macrophages by crosslinking TLR4 and Fc gamma receptors and binding to the macrophage Fcγ receptor IIa in vitro, causing TNFα production. Patients with Anti-CCP and RF had elevated levels of TNFα, IL1β, IL6, and IL17. (12)

Subtypes

JIA classification criteria were proposed by the International League of Associations for Rheumatology (ILAR). The clinical symptoms and HLA-B27 test findings are used to classify JIA into seven subtypes based on ILAR classification criteria: systemic-onset JIA (sJIA), oligoarticular JIA, seropositive polyarticular JIA, seronegative polyarticular JIA, enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (JpsA), and undifferentiated JIA. (15)

The disease subtype should be determined both at the outset of the disease and over the course of the disease. The initial classification is based on the clinical symptoms of the condition during the first six months. **Oligoarthritis** is defined as chronic arthritis that affects four or fewer joints in the first six months of disease. After the first six months, **persistent oligoarthritis** is defined as four or fewer affected joints, while **prolonged oligoarthritis** is defined as more than four affected joints. The ultimate disease subtype is determined by the emergence of new clinical symptoms along the course of the disease. The primary goal of illness subclassification is to homogenise disease groups, identify medication options, select follow-up strategies, and forecast disease prognosis **.** (16)

RF Negative polyarthritis is defined as arthritis affecting five or more joints with a negative IgM RF during the first six months of illness. **RF positive polyarthritis** is defined as arthritis that affects five or more joints in the first six months of disease and has a positive IgM RF on at least two tests three months apart. **Systemic arthritis** is defined as arthritis accompanied by at least one of the following symptoms: evanescent erythematous rash, generalized lymph node enlargement, hepatomegaly and/or splenomegaly, or serositis (pericarditis, pleuritis, and/or peritonitis), with or preceded by a fever of at least a 2-week duration. (17)

Psoriatic arthritis is described as chronic arthritis with psoriasis or chronic arthritis with at least two of the following symptoms in a first-degree relative: dactylitis, nail pitting, onycholysis, or psoriasis. **Enthesitis related arthritis (ERA)** is defined as arthritis with enthesitis, or arthritis or enthesitis with at least two of SI joint tenderness and/or inflammatory lumbosacral pain, a positive HLA-B27, the onset of arthritis in a male over six years of age, acute anterior uveitis, history of ankylosing spondylitis, ERA, sacroiliitis with inflammatory. **Undifferentiated arthritis** is described as chronic arthritis that does not meet the criteria for any subtype or meets the criteria for two or more subtypes. (17)

Systemic JIA (sJIA):

This disease subtype, which is characterized mostly by systemic symptoms, affects both males and females equally and can arise at any time throughout childhood. The condition is defined by the presence of arthritis and intermittent fever for at least 2 weeks, as well as one of the following symptoms: characteristic rash, generalised lymphadenopathy, hepatosplenomegaly, or serositis. Although the frequency varies by geographical region, systemic JIA represents for 10-20% of overall JIA. (18) Once or twice a day, the temperature rises to 39.5 °C. The intermittent fever is usually accompanied by a distinctive, salmon pink-colored rash that appears on the trunk and proximal extremities and disappears, when the fever fades. Polyarticular arthritis, which involves both large and small joints, can occur on occasion during the course of the disease. **(**19**)**

In general, systemic symptoms such as fever and rash fade after the onset of polyarthritis, thus distinguishing it from typical polyarticular JIA can be difficult. **(**20**)** Fever and other systemic symptoms can last for months, but rarely more than six months. One-third of patients have hepatosplenomegaly and lymphadenopathy. Serositis, comprising pericarditis and pleuritis, can occur and cause severe chest pain. During the fever's peak, abdominal discomfort and myalgia may emerge. There may be leukocytosis, hypochromic microcytic anemia, thrombocytosis, acute-phase reactant elevation, and a rise in transaminases. Elevated ferritin levels are associated with sJIA. Autoantibodies, antinuclear antibodies (ANAs), and RF are all negative. **(**8**)**

Osteopenia, osteoporosis, growth retardation, erosive arthritis, and amyloidosis are all possible consequences of sJIA. Macrophage activation syndrome (MAS), a severe and sometimes fatal sJIA consequence, occurs in 5-8% of cases. It is linked to significant morbidity and mortality. There are signs of moderate/severe disseminated intravascular coagulation(DIC) (thrombocytopenia, increased fibrin degradation products

(FDPs), significantly raised levels of D-dimers, delayed prothrombin time (PT), and partial thromboplastin time (PTT)). When there is hypofibrinogenaemia, the erythrocyte sedimentation rate (ESR) drops dramatically. Liver enzymes, lactate dehydrogenase (LDH), triglycerides, and ferritin levels are typically high, occasionally with severe hyperferritinaemia, hypoalbuminaemia, and hyponatraemia **.** (21)

A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation collaborative initiative recently proposed criteria for MAS complicating systemic JIA: febrile patients with confirmed or suspected sJIA with ferritin >684 ng/mL and any two of the following – platelet count ≤181x109/L, aspartate aminotransferase (AST) >48 units/L, triglycerides >156 mg/dL, fibrinogen ≤360 mg/dL. Although demonstration of prominent haemophagocytosis in the bone marrow aspiration represents a valuable finding, it has not been included in MAS diagnostic criteria since haemophagocytosis cannot be documented in the early stage of MAS **.** (22)

The diagnosis of sJIA may be difficult, especially in the early phase of the disease without apparent arthritis. Many conditions should be considered in differential diagnosis of sJIA: infections (septicaemia, bacterial endocarditis, brucellosis, typhoid fever, leishmaniasis, viral infections), malignancies (leukaemia, lymphoma, neuroblastoma), rheumatic fever, connective tissue diseases, Kawasaki disease, Castleman's disease and autoinflammatory . (15)

Oligoarticular Juvenile Idiopathic Arthritis

Oligoarticular JIA is the most prevalent form of JIA in developed nations, and it is most common in female children under the age of six. (16) It is further classified into two subgroups: persistent (no more than four joints affected over the course of the disease) and extended (the total number of affected joints exceeds four after the first 6-month period). (23) In 70-80% of cases, the RF is negative but the ANA is positive. The risk of uveitis is increased in ANA-positive patients. **(24)**

Uveitis, rather than arthritis, is the main disability factor in that patient group. Oligoarticular JIA predominantly involves lower-extremity joints, such as the knee and ankle joint. The hip joint is rarely affected. Small-joint involvement is pretty rare in this entity. (25) Since small-joint involvement could be an early sign of psoriasis, the family history in particular should be assessed in this group**. (26)**

Laboratory indicators of inflammation may be normal, although mild to moderate elevation of the ESR and C reactive protein (CRP) levels may occur during the acute phase of the disease. Elevated ESR and arthritis of upper extremities are more common in patients with extended oligoarticular JIA. Mild anaemia and leukocytosis could be seen in patients with acute arthritis **. (1)**

The disease is characterized by a benign clinical course, in general. However, erosions due to extension to polyarthritis and uveitis are two of the possible severe complications. A significant difference in length between extremities could be seen, depending on the extent of the joint damage. Growth retardation is rare. Although remission is achieved frequently, disease flares may occur many years later; thus, regular follow-up for at least 4-5 years is mandatory **.** (27)

Polyarticular Juvenile Idiopathic Arthritis

Polyarticular JIA is defined as arthritis affecting five or more joints within the first six months of the disease. According to RF positivity, the disease is classified into two subgroups. The disease's prevalence varies by geographical region, with RF-negative polyarticular JIA accounting for 11-30% and RF-positive JIA accounting for 2-10% **(Demirkaya et al, 2011).** Both of the disease subgroups are more common among girls. RF-negative polyarticular JIA displays a biphasic trend with peaks of onset between 2 and 4 years and 6 and 12 years. The RF-positive subgroup is more common in later childhood and adolescence. Furthermore, moderate hepatosplenomegaly and mild growth retardation could develop **. (1)**

Seronegative polyarticular JIA is an entity consisting of three different subgroups. The first one includes an oligoarticular JIA-like condition with the involvement of more than four joints in the first 6 months; the main characteristics of the disease are increased uveitis risk, the development of asymmetric arthritis, early disease onset, female predominance, ANA positivity and association with HLA-DRB1*0801 **.** (15)

The second disease subgroup mimics the RF-negative polyarticular JIA with early disease onset, symmetrical involvement of both small and large joints, ANA negativity and variation in disease prognosis. The third disease subtype shows the worst prognosis with poor response to treatment and frequent disease sequelae . From time to time, the disease can appear with oligoarticular involvement extending to polyarthritis. The arthritis of the small joints of upper extremities, metacarpal-phalangeal joints and the wrist is typically symmetric **.** (15)

Small joint arthritis in the lower extremities could be found, though less commonly. Hip, cervical spine, and shoulder involvement may also be observed. The majority of patients have temporomandibular arthritis, which causes secondary microretrognathia. **(20)** These disease subgroups have a high prevalence of damage, particularly hip joint involvement, which is associated with substantial morbidity and surgical procedures. **(28)**

While large-joint involvement is possible, symmetrical small-joint arthritis is more common. The clinical history of RF-positive polyarticular JIA is similar to that of adult RA**.** (15). Subcutaneous nodules, histologically comparable to RA nodules, may be observed in RF-positive patients. These nodules resolve on their own and are correlated with serum RF levels. The most important predictors of substantial joint injury are RF and Anti-Cyclic Citrullinated Peptide (anti-CCP) positivity. (29)

Middle anemia could be found in polyarticular JIA patients due to continuous inflammation. During the active-disease era, lymphadenopathy and hepatosplenomegaly may accompany the other illness symptoms. Depending on disease activity, growth and development retardation may exacerbate the condition. The transaminase level may rise as a result of disease activity or as a result of the therapy's hepatotoxicity. Transaminase levels decrease in tandem with illness remission**.** (20)

Enthesitis Related Arthritis (ERA):

For the past 25 years, ERA has been one of the most contentious issues in paediatric rheumatology. These patients exhibit symptoms of both JIA and juvenile spondyloarthropathies. For many years, other labels for the same clinical entity were used, such as type 2 oligoarticular JIA, JCA with late onset, seronegative enthesopathy and arthropathy, arthropathy linked with HLA B27, or juvenile spondyloarthropathy with early start **. (1)**

The Durban classification defines the word ERA. After the age of six, males are more likely to develop the condition. The patients' major characteristics are RF and ANA negative, as well as enthesopathy and asymmetric arthritis of the lower extremities. In 65-80% of patients, HLA B27 positive has been found. (30)

Enthesopathy is the inflammation of the tendons' attachment points to the bones. During the same clinical evaluation. **(Weiss et al, 2011)** found enthesopathy in 47% of patients and in three separate sites in 18% of patients. (31)

The Achille' tendon is the most frequently Impacted. The patellar insertion of the quadriceps tendon, as well as the calcaneal and metatarsal insertions of the plantar fascia, may be impacted. Pain and sensitivity are present at the afflicted spot. Enthesopathy, on the other hand, can be seen in a variety of illnesses, including familial Mediterranean fever, Behçet's disease, Osgood-Schlatter syndrome, and fibromyalgia. (32)

Asymmetric oligoarticular lower-extremity arthritis is the most common type of joint involvement, with the knee and ankle being the most typically afflicted. The condition can be triggered by a variety of infections or traumas. The involvement of the hip joints is the most notable difference between this and oligoarticular JIA. At the outset of the condition, patients may experience prolonged arthralgia of the lower extremities. This stage of the disease does not impact the axial skeleton. Nonsteroidal anti-inflammatory drugs (NSAIDs) produce outstanding results, with complete or partial remission. The risk of complications is modest. (32)

Juvenile Psoriatic Arthritis (JpsA):

JpsA is still a controversial topic in pediatric rheumatology. The ILAR criteria defines the condition as arthritis with either a psoriatic rash or two of the following: dactylitis; nail pitting or onycholysis; and psoriasis in a first-degree relative. (15) Because articular involvement usually begins a few years before cutaneous signs, the diagnosis may be difficult. Articular involvement can range from symmetrical small-joint arthritis to asymmetrical lower-extremity large-joint arthritis, and it can eventually proceed to polyarthritis that looks like seropositive rheumatoid arthritis.

Psoriatic arthritis is usually indicated by involvement of the distal interphalangeal joints. Dactylitis is defined as “sausage-like” fingers caused by arthritis of the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints of one or more fingers. ERA symptoms (enthesitis, sacroiliitis, spondylitis, etc.) can be seen in some patients . (33)

Typically, psoriatic plaques are seen on the extensor sides of joints, haired skin, the umbilicus and the perineum. Nail changes, including nail dystrophy, subungual hyperkeratosis and onycholysis are common among patients with psoriasis, albeit being less frequent in patients without arthritis. Increased acute phase markers, anaemia of chronic disease and thrombocytosis could be seen. ANA is found in low or moderate titres in a significant proportion of patients. HLA B27 positivity accounts for 30%. (33)

Laboratory Findings:

There is no specific test for diagnosis and predicting disease activity in JIA. Complete blood count (CBC), ESR, CRP, ANA, RF, anti-CCP antibodies, and HLA-B27 should be included in the initial laboratory assays. Inflammatory indicators are prevalent, particularly in oligoarthritis. A positive RF or anti-CCP test has little diagnostic utility but may suggest a worse disease progression and outcome. When MAS occurrence is suspected, ferritin, fibrinogen, AST, and triglyceride levels should be checked. Depending on the differential diagnosis, various tests for excluding other disorders may be considered**.** (17)

Laboratory tests for HLA-B27, RF or anti-CCP antibody identifies the subtype of JIA and the risk of bone erosions and joint damage. Myeloid-related protein (MRP)8, MRP14 and IL18 may be used as biomarkers for active sJIA, whereas HLA-B27 is predictive of ERA . ANA and RF are useful for the diagnosis of oligo and pJIA subtypes (12) ANA is associated with increased risk of chronic non-granulomatous uveitis, which is the most common extra-articular manifestation of JIA and is typically asymptomatic but has an elevated risk of causing visual impairment. Aljaberi et al. (2020) reported higher levels of pro-inflammatory calcium-binding S100 proteins in sJIA patients compared to other autoinflammatory syndromes. However, other studies have revealed that high baseline S100A12 concentration is associated with higher disease activity and response to methotrexate (MTX) and anti-TNF therapy in patients with JIA including pJIA, ERA, oligoarticular and psoriatic arthritis (34).

Radiology

Imaging is used to increase the certainty of a JIA diagnosis, restrict the differential diagnosis, and assess joint degeneration. Because clinical symptoms are so diverse, a multimodal imaging strategy is frequently required. Radiography is still the first imaging modality used for symptomatic joints; however, radiographic alterations are undetected in the early stages of JIA. Soft tissue edoema, increased soft tissue density, and fat fold displacement are all indirect indicators of arthritis in radiography. Periarticular osteoporosis, joint space constriction, bone erosion and deformity, and joint subluxation or ankyloses are other characteristics**. (35)**

Ultrasound (US) is a non-irradiating imaging technique that plays an important role in the imaging of JIA. In addition, US enables for comparison with the contralateral side as well as dynamic joint examination. US can evaluate synovial thickening, joint effusion, tenosynovitis, enthesitis, and bone erosions. The examination of synovial thickness and synovitis in the US is very significant for diagnosis. They manifest as unusually hypoechoic tissue at joint lines or surrounding tendons. The US accurately recommends for intra-articular corticosteroid injections in addition to diagnosing synovitis. Without sedating the patient, US allows for examination. (35)

Magnetic resonance imaging (MRI) is the gold standard modality for studying JIA. All joints affected by pathological inflammatory events can be investigated simply in all feasible plans and with great bone and soft tissue contrast resolution. It is the most sensitive method of identifying synovitis. T1 spin-echo (SE) sequence, fat-suppressed sequence (traditional T2 fat-sat; short tau inversion recovery – STIR; DIXON fat-suppression sequence); and T1 fat-suppressed sequence precontrast and postcontrast. The only modality capable of objectively detecting bone marrow edoema and the most sensitive to detect bone erosions is MRI. (35)

Diagnosis and Disease Activity Measurement

The diagnosis of JIA is based upon clinical criteria (Table 1). Occasionally, it can take time to establish the definitive diagnosis of the disease, due to the insidious course of the disease. Since there are no laboratory data specific for the disease, patients could be misdiagnosed at disease onset. Laboratory features are useful in differential diagnosis and in defining the disease subclassification. (36)

Table 1: International League of Associations for Rheumatology classification of subtypes of JIA (36)

Type	Definition and Exclusion criteria
Systemic onset JIA	Fever of 2 or more weeks and arthritis in 1 or more joints plus one or more of the following: 1. Evanescent, non-fixed erythematous rash. 2. Generalized lymph node enlargement 3. Hepatomegaly, splenomegaly or both 4. Serositis Exclusion: a, b, c, d
Oligo-arthritis onset JIA	Arthritis affecting 4 joints or less during the first 6 months Exclusion: a, b, c, d, e
Persistent Oligoarthritis	Affecting 4 or less joints throughout the disease.
Extended Oligoarthritis	Affecting more than 4 joints after the first 6 months.
Polyarthritis onset JIA	Arthritis affecting 5 joints or more during the first 6 months
Rheumatoid Factor Positive	RF positive at least 3 months apart. Exclusion: a, b, c, e
Rheumatoid Factor Negative	RF negative Exclusion: a, b, c, d, e
Psoriatic Arthritis	Arthritis and psoriasis, or at least 2 of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first degree relative. Exclusion: b, c, d, e
Enthesitis- Related Arthritis	Arthritis and enthesitis or arthritis or enthesitis , with at least 2 of the following: presence/ history of sacro-iliac joint tenderness &/or lumbo-sacral pain, presence of HLA- B27 Ag, onset of arthritis in male > 6 years old, acute anterior sacroilltis with IBD, Reiter syndrome, or acute anterior uveitis
Undifferentiated Arthritis	Fulfills none of the above subsets or fulfills more than one of them.
Exclusion Criteria for JIA: (a) psoriasis or history of psoriasis in the patient or his first- degree relatives (b) Arthritis in an HLA- B27- positive male beginning after the 6th birthday (c) Ankylosing Spondylitis; enthesis- related arthritis; sacroillitis with IBD; Reiter syndrome; or acute uveitis (d) Presence of IgM RF on at least 2 occasions at least 3 months apart (e) Presence of systemic JIA in a patient	

Many different instruments for measuring JIA disease activity have been established: Juvenile Arthritis Functional Assesment Report, Juvenile Arthritis Functional Assesment Scale, Juvenile Arthritis Disease Activity Score (JADAS). Furthermore, Childhood Health Assesment Questionnaire (CHAQ) and. Paediatric Quality of Life Inventory were developed with the intention of incorporating estimates of physical, social and mental functioning into health assessment. Among numerous available instruments for JIA, CHAQ and JADAS are most

widely used in routine practice. The American College of Rheumatology proposed measurements consisting of five items that are used in the assessment of disease activity in JIA patients.

The monitoring of disease activity is another important topic in the follow-up of JIA patients. Various measures (e.g., parent/patient visual analogue scale, physician visual analogue scale, number of active joints, anaemia, thrombocyte count, ESR, Steinbrocker score, etc.) are used to quantify disease activity, although none of them have been proved to be completely accurate The monitoring of disease activity is another important topic in the follow-up of JIA patients. Various measures (e.g., parent/patient visual analogue scale, physician visual analogue scale, number of active joints, anaemia, thrombocyte count, ESR, Steinbrocker score, etc.) are used to quantify disease activity, although none of them have been proved to be completely accurate. (1)

Table 2: Instruments for measurement of JIA disease activity routinely used in clinics for paediatric rheumatology (1)

Padiatric Response Criteria	
ACR Pedi 30, 50, 70, 90, 100 responses	Improvement of 30, 50, 70, 90, 100 % respectively, as compared to baseline values in at least 3 of the 6-item set, accompanied with no worsening of 30% even in 1 item set.
ACR Pedi item set	1. General evaluation of the disease efficiency, physician VAS (10 cm visual analogue scale) 2. General evaluation of the disease efficiency, parent/ patient VAS (10 cm visual analogue scale) 3. Functional sufficiency – CHAQ 4. Number of active joints 5. Number of joints with limited motion 6. ESR
JADAS	1. General evaluation of the disease efficiency, physician VAS (10 cm visual analogue scale) 2. General evaluation of the disease efficiency, parent/ patient VAS (10 cm visual analogue scale) 3. Number of active joints 4. ESR (Scale 1-10 using the formula (ESH-20)/ 100) If ESR < 20 mm/hr. = 0 If ESR > 120 mm/hr = 120
Definitions of disease efficiency Clinically inactive disease (all 6 sets should be met)	1. No active joint will be present 2. Fever, erythema, serositis, Splenomegaly, diffuse lymphadenopathy will not be preset. 3. No uveitis will be present 4. ESR & CRP will be normal 5. Morning Stiffness will last less than 15 minutes 6. Physician VAS will be the lowest value in the scale used.
Clinical remission with medication	Inactive disease for longer than 6 months under treatment
Clinical remission without medication	Inactive disease for longer than 12 months after the end of treatment
Quality of life measurement tools (CHAQ)	Disease specific measurement tool that evaluates the ability to perform daily activities.
PedsQL	Multi-dimensional child self-report and parent paroxy report scale (includes physical health, emotional and social functionality).

ACR: American College of Pediatric Rheumatology JADAS: Juvenile Arthritis Disease Activity Score PedsQL : Pediatric Quality of Life inventory

Treatment / Management

Chronic inflammation of the joints severely restricts the patient's functional abilities and productivity in daily life. The fundamental cause of the aforementioned issues is uncontrolled inflammation. In addition to joint issues, untreated patients may suffer growth retardation, uveitis, blindness, and life-threatening MAS. Adverse pharmacological effects should also be considered (for example, osteoporosis, growth retardation caused by glucocorticoids, and so forth).Thus, JIA treatment should be quick and successful. (25)

The goal of therapy should be multifaceted: to control pain, to maintain range of motion/muscle strength/muscle function, to induce disease remission, to manage systemic consequences, and to promote normal physical and psychosocial development. The treatment length should be changed every three months until the treatment goal is met. Disease activity should be regularly checked(every 1-6 months). (37) Different instruments are used in disease activity assessment **(Table 2).**

Disease activity indicators should be utilized to establish therapy targets. Furthermore, when determining the optimum therapy target, it is important to consider patient and parent compliance, JIA subtype, and medication-related adverse effects. Children and parents should be thoroughly educated about the procedure and objectives . (37)

JIA treatment includes anti-inflammatory and immunomodulatory medications, as well as physical therapy, and may finally entail surgery, nutritional support, and psychosocial support. The choice of pharmacological treatment is influenced by sickness subtypes, disease severity and damage, comorbidities, and family acceptability. NSAIDs are the first-line therapy for all subtypes. With current aggressive therapy options such as methotrexate and biologics, NSAID use in JIA has decreased over time. Physical therapy focuses on joint mobility while decreasing joint tension. Swimming is often a suitable option. Patients should do light cardiovascular, flexibility, and strength exercises . (17)

NSAIDs:

NSAIDs work by inhibiting cyclooxygenases (COXs), an enzyme that is required for prostaglandin formation. Prostaglandins play physiological roles such as establishing and maintaining the stomach's protective mucosal barrier and encouraging intrarenal plasma flow and electrolyte homeostasis. The family should be informed about the potential gastrointestinal (GI) and nephrotoxicity. (38)

According to a survey of pediatric rheumatologists, nonselective NSAIDs cause much more abdominal pain, easy bruising, epistaxis, headaches, and exhaustion than selective COX-2 NSAIDs. However, there is no difference in the safety profile, including GI toxicity, between nonselective NSAIDs (COX1 and COX2 inhibitors) and selective COX-2 inhibitor (celecoxib). Because over 50% of children with JIA developed gastrointestinal symptoms as a result of NSAID, corticosteroid, or methotrexate use, it is necessary to review the medical history and previous or concurrent use of NSAIDs, corticosteroids, or methotrexate to assess and minimize the potential risk of gastrointestinal toxicity. Acute interstitial nephritis or acute papillary necrosis are examples of possible nephropathy. Children have a nephrotoxicity prevalence of 0.4%, which is five times lower than the prevalence in adults. It is unclear if routine monitoring (blood and urine) of asymptomatic children with JIA who are just receiving NSAIDs is beneficial. (37)

NSAIDs represent the traditional initial approach. Ibuprofen, indomethacin, tolmetin and naproxen are the most commonly used agents. This group of drugs is used particularly in children under 12 years old. In patients with oligoarticular JIA the disease remission could be induced by NSAIDs. The main characteristics of the drugs are their analgesic effect in lower doses and anti-inflammatory effect when used in higher doses. Treatment response is seen in the first 1-3 days with pain relief. This type of drug is considered tolerable in childhood patients, despite the abdominal pain and headache that could occasionally be seen as an adverse effect. (37)

Corticosteroids:

This group of drugs is characterized by the most potent anti-inflammatory activity. However, the usage is limited due to numerous side effects and low efficacy in the prevention of joint destruction. Intra-articular administration (methylprednisolone acetate, triamcinolone hexacetonide) has been shown to be effective in inducing remission in oligoarticular JIA patients, even with a single injection. (39) Oral or parenteral administration of steroids has the ability to abate systemic symptoms in patients with the systemic form of the disease.

Symptoms such as joint pain, swelling, sensitivity or disease-related carditis, hepatitis, lung disease and fever show a significant response to steroid treatment. However, due to numerous side effects, usage in low doses or on alternative days is recommended in patients in whom control of the disease has been achieved. The generally used dose of steroids is up to 1 mg/kg/day. The dose could be increased up to 1-2 mg/kg/day in patients with cardiac insufficiency or tamponade secondary to carditis or pericarditis. Patients with severe clinical presentation of systemic JIA should be treated with a high dose of steroids (30 mg/kg/day) for three consecutive days. (40)

DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs):

Methotrexate:

Most patients show a response in the first 2-3 weeks of treatment. Occasionally, it can take some time to achieve treatment response. Folic acid or folinic acid at a dose of 1 mg/kg/day is used, in order to reduce the adverse effects including bone marrow suppression, nausea, oral ulcerations and hair loss. The fact that folinic acid decreases the methotrexate activity should not be forgotten. (37)

Sulphasalazine:

Different studies have reported the efficiency of sulphasalazine in patients with JIA, especially in the oligoarticular- and enthesitis-related forms of the disease. Treatment response is achieved in 6-8 weeks of treatment, in general. Headache, rash, gastrointestinal toxicity, myelosuppression, hypogammaglobulinemia and allergic reactions are some of the possible adverse effects. The initial dose is 10-20 mg/kg/day, gradually increasing to 50 mg/kg/day in the following few weeks. (41)

Biological drugs:

Inadequate efficacy of medications used in the treatment of JIA for years, as well as the formation of permanent joint restrictions, forced the development of alternative therapeutic options. Despite early intense treatment (early use of methotrexate) employed in the previous 20 years, many pediatric patients in adulthood have persistent active disease. Therefore, biological drugs have been started to be used in treatment of JIA with the objective of reducing the frequency of chronic sequela and achievement of complete suppression. In fact, it is justified to use biological drugs in any child with JIA if there is no response to long-acting drugs at the end of a 3-6-month treatment period. (40)

Tissue macrophages are stimulated in JIA, as they are in all rheumatic illnesses. Following that, an abundance of proinflammatory cytokines is released, resulting in a disturbed helper T cell response. The inflammatory process is caused by cytokines such TNF-alpha, IL-1 and IL-6. TNF-alpha causes synovitis and inflammatory events, IL-1 causes joint degeneration, and IL-6 causes systemic symptoms, such as fever and rash. (42)

This pharmacological class is more commonly used in adults, and its safety has been shown. These medications have only lately begun to be used in children, and their application is limited. Because of the differences in mechanism of action, drug selection should be done by disease subgroup. Furthermore, the patient's preference for manner of administration and frequency of administration should be considered. These medications' limits for use include insufficient long-term safety data and cost, though they are efficient drugs. (46)

Etanercept:

Etanercept is a fusion protein that combines the extracellular ligand-binding region of the human 75 kilodalton (p75) tumor necrosis factor receptor (TNFR) with the fragment crystallizable (Fc) portion of human immunoglobulin (Ig) G1. The molecule binds to soluble TNF-alpha (α), inhibiting downstream TNFR-mediated

signaling. Etanercept is a biological medication with demonstrated efficacy and safety in JIA patients, particularly those with the pJIA subtype . (44)

Etanercept is very efficient especially on peripheral joint arthritis. It is the most efficient treatment option in patients with polyarticular JIA. A dose of 0,8mg/kg/week was shown to be efficient and safe in other studies. The efficiency of the drug occurs prominently after the second or third dose . (45)

Drug responses are rarely recorded in general. The most often reported medication responses are minor infections that do not necessitate hospitalization. The most common non-infectious adverse effects are local skin responses at the injection site . (44) Aside from frequent, moderate injection-site responses, the most common adverse event among JIA patients treated with etanercept were neuropsychiatric manifestations. (46)

Infliximab:

Infliximab (Remicade) is an anti-TNF human/mouse chimeric monoclonal antibody. It binds to all TNF-alpha receptors on the cellular surface. In contrast to etanercept, infliximab affects both soluble TNF receptors and TNF receptors found on the cellular surface. Its efficiency in treatment of JIA has been demonstrated. In contrast to the other drugds, it is administered at a dose of 3–6 mg/kg (maximum dose 100 mg) intravenously every 4-8 weeks . (47)

It is used to treat a wide range of pediatric inflammatory diseases, including JIA, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, ulcerative colitis, and uveitis. (48) Furthermore, the frequency of severe and opportunistic infections was unremarkable in studies including individuals treated with infliximab. However, allergic responses after an intravenous (IV) infusion of infliximab appear to be slightly more likely than with other TNF blockers. (37)

Interleukin-1 antagonists

Anakinra:

Anakinra is generally tolerated well and severe side effects are observed rarely. Its disadvantage is requirement of daily injections and itchy rash may be observed in the injection site. Although the rash spontaneously improves in time, improvement can be provided more rapidly with cold application. Rare cases of neutropenia and hepatotoxicity have been reported. (49) The injection site reaction is the most prevalent adverse effect, which can sometimes make its use problematic. Nonetheless, it is a well-tolerated and easily accessible therapy with demonstrated efficacy in sJIA patients. (50)

Rilonacept:

Rilonacept eliminates the efficiency of IL1 receptor protein by acting as a recombinant fusion protein. The dose of usage is 2,2-4,4 mg/ kg/week. In a double-blind placebo-controlled study, good response was obtained in patients diagnosed with sJIA **. (51)** Although it is not recommneded for the initial treatment of systemic JIA, it is recommneded in cases of unresponsiveness to the other Il-1 antagonists and active disease and active arthritis. **(52)**

Kanakunimab

Kanakunimab (Ilaris), a monoclonal immunoglobulin (Ig) G1 antibody, reduces molecular efficiency by acting as an isoform of IL-1β. Phase II trials have demonstrated its efficacy in patients with systemic JIA .It was authorized by the FDA in the United States in 2013 for the treatment of active systemic JIA in individuals aged two and up. In a study systemic JIA patients showed a significantly higher response in terms of ACR pedi 30 response and fever reduction (84%, 10%) compared to placebo. The suggested dose is 4 mg/kg/every 4-8 weeks for children under 40 kg and 150 mg/kg/every 8 weeks for those over 40 kg. No cancer, TB, or other opportunistic infections **. (53)**

Interleukin-6 antagonist treatment

Tosilizumab:

Tosilizumab (Actemra) is a monoclonal IL−6 receptor antibody. It acts by binding to IL-6 receptor (IL-6R) and eliminating IL-6-IL6R bound. In systemic JIA, serum IL-6 levels are related with CRP and fever. In a double-blind, placebo-controlled study conducted with 56 patients diagnosed with systemic JIA, treatment response was observed initially in 91% of the patients**. (54)**

Tosilizumab was found to be appropriate for children aged 2 years and older with a diagnosis of active systemic JIA. It may be used alone or in combination with methotrexate. The dose of usage is 12 mg/ kg/2-4 weeks below 12 kg and 8 mg/kg/2-4 weeks above 12 kg. **(55)** Double-blind, placebo-controlled studies conducted with tosilizumab showed that there was no significant increase in the risk of infection and no cases of tuberculosis and other opportunistic infections were found. Neutropenia, thrombocytopenia, increased low density lipoprotein, increased alanine aminotransferase (ALT) and AST levels were found with a higher rate in the patients with systemic and polyarticular JIA who were using tosilizumab. (56) It was approved by FDA for treatment in cases of systemic JIA unresponsive to previous treatments and especially in cases of active arthritis which do not show improvement and in polyarticular JIA. **(52)**

Treatments targeting T cells and B cells T

Abatacept:

Abatacept is thought to work by inhibiting CD28 costimulation, which interferes with T cell-APC interactions and limits T cell activation **. (57)** Abatacept has been approved by the FDA for patients over the age of six with polyarticular JIA since 2008. The medicine is administered as monthly injections at a dose of 10 mg per kilogram. A double-blind, randomized study of 190 children with polyarticular JIA demonstrated abatacept's efficacy. In this study, abataceptin (20%, 12/60) was found to be considerably more effective than placebo (53%, 33/62) **. (58)**

In the long-term, open-label portion of this trial, the rates of ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, and ACR Pedi 100 were discovered to be 90%, 88%, 57%, and 39%, respectively. In the long run, it was found to be effective and free of serious adverse effects. There were no reports of cancer or tuberculosis infections. However, multiple sclerosis was discovered in one patient **. (59)**

Rituksimab:

RTX is a therapy option for active, severe JIA that does not respond to DMARDs or anti-TNF blockers **. (60)** The drug is administered as four infusions weekly at a dose of 375 mg/m^{2}'. This treatment can be repeated three or four times, if necessary. Before treatment with rituksimab, meningococcus, pneumococcus and influenza vaccinations should absolutely be completed. (37)

Tofacitinib/CP-690,550:

Tofacitinib/CP-690,550 is a selective JAK inhibitor. Tofasitinib acts by inhibiting the activation of JAK 1, JAK 2 and STAT 1. It was approved by FDA for treatment of rheumatoid arthritis. (61) Open-label studies are continuing for its use in treatment of juvenile idioptahic arthritis**. (62)**

Side effects of biological drugs

The higher risk of infection among JIA patients has been reported independently of biological use. It is believed that the disease's pathophysiology increases the danger of infection.**(63)**As a result, adverse events (especially infections) from biologics in JIA patients should be closely monitored and understood. It is widely believed that the increasing incidence of infections is caused by a combination of factors, including disease etiology, immunosuppressive treatment (both biological and non-biological), and socioeconomic factors **. (64)**

Malignancy was reported by FDA for the first time in 2008 in a few patients who were receiving biological treatment for JIA. There are controversial views about this report, because immunosupressive drugs used in combination with biological drugs might have contributed to this outcome and there is no clear data about the frequency of malignancy in JIA . Although it has been proposed that there might be a relation between JIA treatment and development of cancer, a direct causal relationship between biological agents and malignancy has not been established yet . (64) Secondary malignancy did not develop in any of more than 300 patients who used biological drugs and who were followed up by our group. It is important to evaluate if the patients have used precancerous drugs and if there is a familial history of cancer before treatment with these drugs . (65).

Conclusively, it was observed that biological drugs were considerably efficient and safe in treatment of JIA in the light of all this information. The biological drugs used in treatment of JIA have significantly changed the course of JIA. These children will use less medication and especially less steroid, require less surgical treatment, their education will be hindered less and they will be psychologicaly healthier active individuals. Considering

the cost of these drugs, indications for use should be evaluated efficiently. However, frequent and meticulous monitoring of patients is especially important, since there are no long-term results for pediatric patients.

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