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Contemporary strategies in the diagnosis and treatment of juvenile jdiopathic arthritis: imaging techniques and therapeutic advances

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ABSTRACT:

Introduction and purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in children, involving not only joints but also internal organs, skin, and eyes. It is diagnosed in children under the age of 16 when symptoms last longer than six weeks. The ILAR classification includes several subtypes such as oligoarticular, polyarticular (RF-positive and RF-negative), systemic (sJIA), psoriatic, and enthesitis-related arthritis. Systemic JIA is characterized by fever and rash, while the oligoarticular form often coexists with positive ANA antibodies and carries a high risk of chronic uveitis. New subtypes have been added in recent years, such as early-onset ANA-positive JIA. Imaging, including X-ray, MRI, and ultrasound, plays a crucial role in assessing disease progression, especially in the hip, knee, and temporomandibular joints. Treatment involves a multidisciplinary approach and includes NSAIDs, intra-articular and systemic glucocorticoids, non-biologic DMARDs (especially methotrexate), and biological therapies. Biologic agents include TNF inhibitors (adalimumab, etanercept, infliximab), IL-1 inhibitors (anakinra, canakinumab), IL-6 inhibitor (tocilizumab), T-cell inhibitor (abatacept), and B-cell therapy (rituximab). These targeted treatments improve disease control, reduce joint damage, and enhance quality of life, enabling many patients to achieve remission and prevent long-term disability.

Summary: The aim of the article is to categorize and provide an overview of the clinical features of juvenile idiopathic arthritis (JIA), the most common chronic rheumatic disease in children. It presents the classification of JIA subtypes, emphasizing their distinct symptoms, prognostic value, and importance for treatment selection. The article also highlights the role of imaging studies (X-ray, MRI, USG) in early diagnosis and monitoring joint damage, particularly in the hip, knee, and temporomandibular joints. Additionally, it outlines current treatment strategies, including NSAIDs, glucocorticoids, conventional DMARDs like methotrexate, and modern biological therapies targeting inflammatory pathways, underlining the need for individualized, multidisciplinary care to prevent complications and improve long-term outcomes.

Keywords: Juvenile Idiopathic Arthritis, ILAR classification, oligoarticular JIA, polyarticular JIA, systemic JIA, ANA, uveitis, enthesitis-related arthritis, psoriatic arthritis, DMARDs, biological therapy, TNF inhibitors, IL-1 inhibitors, IL-6 inhibitor, glucocorticoids, MRI, ultrasound, X-ray.

INTRODUCTION AND OBJECTIVE

Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease. It is a joint inflammation occurring in children, being the most common rheumatologic condition in this age group, with

an incidence rate ranging from 16 to 150 cases per 100,000 children. This disease can also affect other organs, such as the skin, eyes, and internal organs. [1,2,3]

The etiology and detailed pathogenesis of juvenile idiopathic arthritis (JIA) remain unknown. The disease manifests before the age of 16 and persists in one or more joints for a minimum of six weeks. [1,2,4]

Early diagnosis of JIA and the implementation of appropriate treatment are crucial for improving prognosis. Despite advances in therapy, a significant proportion of children still suffer from permanent physical disability or experience death. This is a consequence of later complications associated with chronic synovitis. [2,3,4]

The chronic nature of JIA and the risk of permanent complications have a significant impact on the lives of affected individuals and their families, deteriorating the quality of their daily functioning. [3,5,6]

1. JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis refers to all chronic inflammatory joint diseases in children. It is the most common chronic rheumatic disease of unknown etiology occurring in childhood. This JIA affects not only the joints, but also the periarticular areas. JIA can attack, among others, the eyes, internal organs, and skin. JIA is diagnosed in children under 16 years of age and when symptoms persist for more than 6 weeks. Advanced stage or lack of proper treatment can lead to disability or even death. [1,2,4,6]

Many new drugs have been developed over the past 15 years, which have significantly improved treatment outcomes. Treatment requires cooperation of many specialists - a pediatric rheumatologist, an ophthalmologist, an orthopedist, a physical therapist, and a child psychologist. The primary goal of treatment is to remove active disease and prevent long-term joint damage. [7,8]

2. CLASSIFICATION

The classification of JIA subtypes is based mainly on the number of affected joints, the presence of symptoms, and the presence or absence of rheumatoid factor (RF) - this is the classification according to the International League of Associations for Rheumatology (ILAR). [1,9,10,11]

Sub-forms of JIA:

- oligoarticular (persistent or extended)
- polyarticular (RF-negative or RF-positive)
- systemic (sJIA)
- psoriatic arthritis
- enthesitis-related arthritis. [1,9,10]

Identifying the subtype is very important because it is related to choosing the right treatment and the patient's prognosis. [7,11]

The initial classification is based on the clinical picture observed during the first six months of the disease. The final subtype of JIA is determined by the symptoms that may appear in the further course of the disease. [7,9]

We diagnose an undifferentiated subtype when the symptoms and other factors do not fit into any other category or correspond to more than one subtype. [1,11]

2.1 Oligoarticular juvenile idiopathic arthritis

When the inflammation affects up to four joints, it is asymmetric (mainly the lower limb joints - knee and ankle), often co-exists with positive antinuclear antibodies (ANA) and is associated with a high risk of chronic uveitis - we can classify MIZS as the oligoarticular subtype. [1] It often occurs in young women. [7,9]

2.2 Polyarticular juvenile idiopathic arthritis

Polyarticular JIA affects five or more joints. Both small and large joints can be affected. A characteristic feature is the occurrence of damage to the metacarpophalangeal and wrist joints. In the case of RF-negative pJIA, inflammation occurs asymmetrically, while in RF-positive pJIA, it occurs symmetrically. In RF-positive pJIA, small and large joints of the hands and feet are most commonly affected. [1,9,11]

2.3 Systemic juvenile idiopathic arthritis

In contrast to other subtypes, systemic juvenile idiopathic arthritis (sJIA) is characterized by systemic inflammatory symptoms. This is the most common subtype of the disease, characterized mainly by recurrent fever and rash. [1,7,12]

2.4 Psoriatic juvenile idiopathic arthritis

Psoriatic JIA is characterized by a psoriatic rash. It is a heterogeneous disease entity whose clinical picture varies depending on the child's age. In children under 6 years of age, the disease affects girls more often, is associated with the presence of antinuclear antibodies (ANA), and increases the risk of chronic uveitis. In this age group, inflammation of the wrists and small joints of the hands and feet is observed. However, in older children, psoriatic JIA is more common in boys and is associated with the presence of HLA-B27 antigen. In this form, enthesopathies and involvement of axial joints are common. [1,7]

2.5 Enthesitis-related arthritis

Enthesitis-related arthritis (ERA) is similar to the oligoarticular subtype. A characteristic feature of this subtype is the occurrence of inflammation in the lower limbs and additionally, inflammation of the tendon attachments. [1,7]

2.6 Changes in classification

In 2019, the Pediatric Rheumatology International Trials Organization (PRINTO) Consensus added a subtype called early-onset ANA-positive JIA. The onset of the disease occurs before the age of 6, mainly in girls. The following characteristics are present: symmetrical inflammation of the joints, iritis and cyclitis, antinuclear antibodies, and a positive HLA-DR8 test result. [1,13]

PRINTO points out that juvenile idiopathic arthritis (JIA) is not a single disease, but a collection of different diseases that do not have to meet the classical criteria based on the number of joints involved or the presence of arthritis itself. Additionally, the age threshold for diagnosis has been extended to include patients under the age of 18. [1]

3. IMAGING STUDIES

Radiographic assessment of joint changes constitutes an important tool in determining the severity and progression of disease in children with juvenile idiopathic arthritis (JIA). Numerous studies have demonstrated that a significant proportion of young patients with chronic arthritis exhibit substantial abnormalities detectable on imaging. In a large group of children, joint space narrowing (JSN) and erosions are already observed in the early stages of the disease. [14,15]

Until recently, standardized and quantitative assessment of radiographic joint damage in juvenile idiopathic arthritis (JIA) has been challenging due to the lack of scoring systems specifically designed for the pediatric population. In recent years, efforts have been made to develop new radiographic assessment tools or to adapt existing methods to the specific characteristics of JIA. However, the majority of proposed scoring systems focus mainly on evaluating changes in the hand and wrist joints. [14,15]

3.1 Diagnostic methods in the hip joint area

Pathological changes in the hip joint are often observed in the most severe forms of juvenile idiopathic arthritis (JIA), affecting approximately 30-50% of children. The hip joint plays a key role in daily functioning, such as weight-bearing. In some cases, hip joint inflammation can progress very rapidly and aggressively, which is why changes occurring in this joint should serve as a warning that the child may become disabled in the future. The greatest susceptibility to early joint space narrowing (JSN) in the course of JIA is seen in the wrist joints, followed by the hip joints. In the natural course of the disease, destructive changes in the hip joint were revealed in the majority of patients with chronic arthritis within 5 years. The appearance of inflammatory changes in the hip joint is considered a marker of poor prognosis in systemic JIA. The traditional radiograph remains one of the most important tools for assessing the course and prognosis of hip disease in JIA, despite the increasing popularity of newer, more sensitive imaging methods such as magnetic resonance imaging (MRI) and ultrasound (USG). [14,16]

3.2 Diagnostic methods in the temporomandibular joint area

The temporomandibular joint involvement occurs in 40-93% of cases of juvenile idiopathic arthritis (JIA). During the research, the highest rate of involvement of the temporomandibular joint was found in polyarticular JIA. [17] However, this joint rarely exhibits distinct signs of inflammation. Despite the presence of radiological changes, the disease in this joint often presents with mild symptoms or is asymptomatic, which complicates early diagnosis. [18]

Chronic temporomandibular joint (TMJ) arthritis in the course of rheumatic diseases is defined as "active temporomandibular joint inflammation" according to the international expert consensus (TMJaw). Diagnosis is based exclusively on the presence of inflammatory changes in the soft tissues as visualized by contrast-enhanced magnetic resonance imaging (MRI). Subjective symptoms and clinical presentation are not taken into account in establishing the diagnosis. The severity of joint involvement may include synovitis, osseous destruction, complete condylar head resorption, and TMJ ankylosis. [18]

In the early stages of the disease, symptoms may include pain in the joint area, joint sounds such as clicking or crepitus, and restricted mandibular mobility. Progressive resorption of the condylar head and cartilage may result in significant facial deformities and malocclusion.

Limited mouth opening and the development of joint ankylosis can severely impair daily functions such as speaking and eating. [18]

The disease course is variable and typically characterized by alternating periods of exacerbation and remission. In approximately 60% of patients with juvenile idiopathic arthritis (JIA), TMJ arthritis becomes inactive by adulthood. Major risk factors for TMJ involvement include long disease duration, high level of disability, early disease onset (particularly before the age of 4), as well as the polyarticular and systemic subtype. TMJ arthritis is more common in females, who are three times more likely to be affected than males. [18]

3.3 Diagnostic methods in the knee joint area

The most frequently affected joint in the course of juvenile idiopathic arthritis is the knee joint, which may serve as an indicator of disease progression and treatment efficacy. The primary clinical manifestations of knee joint involvement include pain, increased skin temperature, swelling, and restricted joint function. [15]

One of the late complications of JIA is erosive joint damage, which may lead to progressive narrowing of the joint space. Although rare, axial joint deformities and ankylosis can also occur, posing significant functional impairment anddiscomfort. [15]

In clinical practice, the imaging study frequently performed when juvenile idiopathic arthritis is suspected is plainradiography (X-ray). This modality enables the evaluation of the extent of cartilage and bone damage; however, it doesnot provide information on active inflammation. It also allows for the identification of growth disturbances and facilitatescomparative analysis of joints—an advantage over magnetic resonance imaging (MRI) and ultrasonography (USG). [15]

4. TREATMENT IN JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) represents a heterogeneous group of chronic inflammatory diseases that begin before the age of 16 and can lead to significant disability if not appropriately

managed. [19] The clinical presentation varies widely among subtypes, ranging from mild oligoarticular involvement to severe systemic inflammation with multi-organ manifestations. [20] Timely diagnosis and a structured treatment approach are essential to control disease activity, prevent joint damage, and support normal growth and development. [7]. Advances in understanding immunopathogenesis have contributed to the evolution of targeted therapies and a more personalized management paradigm. [18]

Non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, indomethacin, tolmetin, and naproxen are commonly the first-line treatment for juvenile idiopathic arthritis (JIA), especially in children under 12. They provide pain relief at low doses and anti-inflammatory effects at higher doses, often reducing symptoms within 1 to 3 days. [7] NSAIDs work by inhibiting cyclooxygenase-1 and -2 enzymes, thereby decreasing prostaglandin production. [21] According to the 2011 American College of Rheumatology guidelines, NSAID monotherapy for 1 to 2 months is recommended for oligoarticular and polyarticular JIA, and they may be continued alongside non-biologic or biologic DMARDs. A trial comparing naproxen and meloxicam in children with JIA found no significant difference in efficacy. Interestingly, some patients respond to a different NSAID after failing one, suggesting a trial of alternatives can be helpful. The main side effects are gastrointestinal, but overall, NSAIDs are well tolerated in children with fewer serious adverse effects than in adults. [21]

Glucocorticoid joint injections are frequently used as first-line therapy for active arthritis in oligoarticular juvenile idiopathic arthritis (JIA) or as second-line treatment after NSAIDs. They are also employed alongside non-biologic or biologic DMARDs when only a few joints remain active. Clinical improvement can last at least 4 months, and injections may be repeated afterward. Long-acting corticosteroids such as triamcinolone hexacetonide are preferred over triamcinolone acetonide due to superior efficacy. Anesthesia is often required, particularly in younger children or when multiple joints are injected. Potential adverse effects include skin atrophy, discoloration, and systemic corticosteroid exposure. [21]

High-dose systemic glucocorticoids are sometimes necessary but can lead to increased bone resorption and osteoporosis risk. They also interfere with growth by disrupting the GH/IGF-1 axis, potentially impairing height in children. [22] Additionally, prolonged use antagonizes insulin action by stimulating hepatic gluconeogenesis and reducing peripheral glucose uptake,

resulting in hyperglycemia and insulin resistance. This metabolic disturbance can worsen inflammation and diminish treatment efficacy. Children with systemic JIA, especially those overweight or obese, are at heightened risk of developing diabetes mellitus due to increased insulin resistance. [19]

4.1 Non-Biologic DMARDs

Methotrexate

Methotrexate remains the first-line DMARD for JIA and is a folic acid analogue that inhibits dihydrofolate reductase, disrupting purine synthesis and DNA production. Its anti-inflammatory effects are partly due to increased adenosine levels. Methotrexate is indicated for oligoarticular and polyarticular JIA with high disease activity or poor prognostic features, typically after NSAIDs and/or intra-articular steroids. It is also part of consensus regimens for systemic JIA [23].

Clinical trials have shown methotrexate is effective, with up to 63% of patients achieving significant improvement compared to placebo. It is usually well tolerated, though gastrointestinal symptoms, oral ulcers, and infection risk can occur. Liver and hematologic toxicity require monitoring of blood counts, liver enzymes, and creatinine every 12 weeks. [21] The usual dose is 10–15 mg/m²/week or 0.5–1 mg/kg/week, with folic or folinic acid supplementation (1 mg/day) recommended to limit side effects like marrow suppression and nausea. Note that folinic acid may reduce methotrexate efficacy. [7]

Leflunomide

Leflunomide inhibits pyrimidine synthesis, reducing lymphocyte proliferation and cytokine production. In trials comparing it to methotrexate, methotrexate achieved higher ACR Pedi 30 responses (89% vs. 68%). [7] However, leflunomide is still considered an alternative for polyarticular JIA, especially when methotrexate fails or is not tolerated. Routine lab monitoring is needed due to risks of liver toxicity and cytopenias. [24]

Sulfasalazine

Sulfasalazine has anti-inflammatory actions via inhibition of prostaglandin and leukotriene synthesis and is recommended for enthesitis-related JIA after NSAIDs or steroid injections. [7] Randomized studies confirmed its efficacy in oligoarticular and polyarticular JIA, with sustained benefits observed long-term. [25] However, side effects like gastrointestinal intolerance, rash, cytopenias, and oral ulcers can lead to discontinuation in nearly 30% of patients. Regular lab monitoring is required during therapy. [7]

4.2 Biological DMARDs

TNF inhibitors

Adalimumab is a subcutaneously administered recombinant human IgG1κ monoclonal antibody that neutralizes TNFα by binding to both its soluble and membrane-bound forms. It is indicated for patients with juvenile idiopathic arthritis (JIA) who are resistant or intolerant to methotrexate, including those with polyarticular JIA, JIA-associated uveitis, enthesitis-related arthritis refractory to sulfasalazine, and psoriatic JIA [26]. Potential adverse effects include an increased risk of reactivation of latent infections such as tuberculosis, as well as new infections caused by viruses, fungi, or bacteria. Rarely, cases of lymphoma, demyelinating disorders of the central nervous system, and congestive heart failure have been reported. [20]

Etanercept is a soluble fusion protein combining the human TNF receptor p75 with the IgG1 Fc fragment. It binds soluble TNFα, inhibiting proinflammatory signaling. Etanercept is highly effective for polyarticular juvenile idiopathic arthritis (JIA), especially in patients unresponsive to methotrexate [27]. The recommended dose is 0.8 mg/kg subcutaneously once weekly, with

clinical improvements usually seen after the second or third injection. [7].Randomized trials have shown significant reductions in disease flares and high ACR Pedi response rates, with up to 80% achieving ACR Pedi 30. Long-term studies confirm sustained efficacy. Better outcomes are associated with early disease onset, prior DMARD use, and lower baseline disability, while systemic JIA and female sex predict lower response. [19] The most common adverse effect is injection site reaction, requiring rotation of injection sites. Mild respiratory infections may occur, but serious infections are rare. Studies in children under 4 years have also demonstrated good safety and efficacy. Central nervous system events such as headache and neuritis, varicella infections, and, rarely, malignancy have been reported. [20]

Infliximab is a chimeric monoclonal antibody with high affinity for TNFα, binding both its soluble and membrane-bound forms. Unlike etanercept and adalimumab, infliximab is administered intravenously at a dose of 3–6 mg/kg every 4–8 weeks, up to a maximum of 200 mg per infusion . It has demonstrated efficacy in the treatment of JIA, particularly in patients with spondyloarthropathies, inflammatory bowel disease, psoriatic arthritis, and uveitis [7]. Combination therapy with methotrexate is recommended to reduce the development of anti-drug antibodies and to enhance therapeutic response. In a randomized placebo-controlled trial in polyarticular JIA, no significant difference in ACR Pedi 30 response was observed initially; however, during long-term open-label extension, 44% of patients achieved an ACR Pedi 30 response at week 204. Although mild upper respiratory infections are relatively common, the incidence of serious and opportunistic infections is similar to other TNF inhibitors. Infusion-related allergic reactions occur more frequently compared to other agents in this class and require monitoring during administration. [21]

IL1 inhibitors

Anakinra is a recombinant human IL-1 receptor antagonist given by subcutaneous injection at 2–10 mg/kg daily (up to a 200 mg maximum). Because IL-1 is a key driver in sJIA pathogenesis, multicenter trials have confirmed anakinra's efficacy and safety in this condition. In a multicenter series assessed of 46 sJIA patients treated first-line with anakinra plus steroids and/or other DMARDs, about 60 % achieved complete remission with normalized laboratory

values and no need for further therapy; fever and rash resolved in over 95 % by one month, and 61 % had no active arthritis after a mean follow-up of 14.5 months.Some patients experience injection-site pain and local reactions, which can complicate its use. Overall, anakinra is well tolerated, with serious infections occurring only infrequently. [7,21]

Canakinumab is a fully humanized monoclonal antibody specifically targeting IL-1β, administered every 4–8 weeks (4 mg/kg in children <40 kg, 150 mg in heavier patients). In an open-label, multicenter study of 25 patients with active sJIA, 60% of patients achieved a modified ACR Pedi 30 response – defined by, among other things, resolution of fever and improvement in six other clinical and laboratory parameters. In two additional randomized, double-blind, placebo-controlled studies, a single dose of canakinumab induced a modified ACR Pedi 30 response in 84% of treated patients, compared to 10% in the placebo group. Respondents from these trials then enrolled in a 32-week open-label extension, during which 74% of patients remained free of disease flare, compared to only 25% in the placebo group. Due to its long half-life and less frequent, milder local reactions, canakinumab is sometimes preferred as first-line therapy for sJIA, although studies indicate a slightly increased rate of infection compared to placebo.[7,21]

IL6 inhibitors

Tocilizumab is a recombinant, humanized monoclonal antibody directed against the IL-6 receptor. It is used in children with active sJIA – alone or in combination with methotrexate or glucocorticosteroids – particularly when joint disease is unresponsive to other treatments, as well as in polyarticular JIA [28]. The dose is 12 mg/kg every 2–4 weeks in patients weighing less than 12 kg and 8 mg/kg every 2–4 weeks in heavier children. Placebo-controlled studies have not shown a significant increase in the incidence of infections, including tuberculosis or opportunistic infections, although it should be noted that tocilizumab may mask the symptoms of infection (by reducing acute phase markers and febrile response). In a randomized study of refractory sJIA patients, 91% achieved an ACR Pedi 30 response after three doses administered over 6 weeks, and in a 144-week extension study, 83.9% of patients maintained this response, with 57.1% remaining clinically asymptomatic. A recent double-blind study by De Benedetti

et al. confirmed that after 12 weeks, 85% of tocilizumab-treated patients met the modified ACR Pedi 30 criteria (compared to 24% in the placebo group), and after one year, approximately half of patients were free of active arthritis and could discontinue glucocorticoids. The most commonly observed adverse events include susceptibility to infections, neutropenia, and elevated aminotransferases. [7,21]

T-cell inhibitors

Abatacept is a soluble CTLA-4 fusion protein with an IgG Fc fragment that binds to CD80/CD86 on antigen-presenting cells, inhibiting the costimulation necessary for the activation of naive T cells. This drug is recommended for patients with polyarticular JIA who have persistent moderate or high disease activity after at least four months of TNF inhibitor therapy (and after a trial of a second TNF inhibitor), as well as for severe JIA [29]. In a randomized, double-blind, withdrawal study (with an open-label run-in phase), children with JIA refractory or intolerant to at least one DMARD received abatacept for four months; 72% of patients achieved an ACR Pedi 30 response. Responding children continued abatacept and experienced fewer exacerbations and reported a significant improvement in quality of life compared to the placebo-withdrawal group. In the 21-month extension study, 90% of patients remaining on abatacept (with or without methotrexate) maintained their ACR Pedi 30 response. Abatacept is well tolerated; the most common events are bacterial and opportunistic infections and infusion reactions, while acute lymphoblastic leukemia is rarely reported. Before administering the drug, patients should be protected with vaccinations against encapsulated bacteria. [21,30]

Anti-B-cell therapy

Rituximab is a humanized monoclonal antibody against the CD20 antigen that leads to the elimination of mature B lymphocytes from the circulation. It is indicated for patients with polyarticular JIA who have failed to respond to treatment with TNF inhibitors and abatacept with high disease activity [31] In an RCT in patients with rheumatoid arthritis refractory to anti-TNF therapy, the addition of rituximab to methotrexate resulted in significantly higher ACR 20, 50, and 70 scores compared to placebo. Alexeeva and colleagues evaluated multiple courses of

rituximab in severe, refractory JIA, achieving an ACR Pedi 30 response in 98% of patients at week 24 and an ACR Pedi 70 response in 93% at week 96 of therapy. The standard protocol calls for the administration of 375 mg/m² of rituximab in three or four doses. The most common adverse reactions include infusion reactions, neutropenia, and decreased immunoglobulin levels. Vaccination against infections caused by encapsulated bacteria is necessary before starting treatment. Data on the use of rituximab in children with JIA are still scarce, although available reports indicate its potential effectiveness. [7,21]

Summary

Our work was aimed at proving Juvenile idiopathic arthritis (JIA) with current research and treatment approaches, demonstrating how recent advances have reshaped the clinical management of JIA. Multidisciplinary care remains essential, involving pediatric rheumatologists, radiologists, ophthalmologists, and allied health professionals. Close monitoring and individualized treatment adjustments are vital to address disease progression and minimize complications.

In summary, we hope this helped summarize current procedures for diagnosing, imaging, and managing JIA, while highlighting the importance of early intervention and personalized therapy. Continued research and clinical collaboration will be key to refining classification systems and expanding treatment success across all JIA subtypes.

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Author's contribution:

Conceptualization: Sandra Czyż, Nina Saracen; methodology: Nina Saracen, Sandra Czyż; software:Karolina Nowak; check: Wiktoria Mistarz; formal analysis: Wiktoria Marszał, Nina Saracen; investigation: Sandra Czyż, Oliwa Sysło; resources: Karolina Nowak; data curation:

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Since this is a review paper, our work does not contain new data or analyses. Consequently, there are no particular databases or data accessibility to outline. The details and conclusions presented in this review are derived from previously published studies, which can be accessed through their respective sources as mentioned in the reference section

Conflicts of Interest Statement:

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