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Overview on Juvenile Idiopathic Arthritis: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is a broad term that refers to a clinically heterogeneous group of arthritis that develops before the age of 16 and has no recognized cause. JIA treatment has evolved during the last two decades. Clinical trials research has been directed at more specific therapeutics based on what has been discovered about the biology of disease. Pediatric rheumatologists now have many more medications to offer patients, with the expectation that their disease will be managed, thanks to advances in immune system research and the introduction of biologic drugs in the twenty-first century. Continuing development in these biological agents and discoveries new drugs as long as developing current gene analysis techniques is the best method to treat JIA and provide best quality of life.

Keywords: Juvenile idiopathic arthritis; oligoarthritis; polyarthritis; rheumatic disease.

1. INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a broad term that refers to a clinically heterogeneous group of arthritis that develops before the age of 16 and has no recognized cause. [1] JIA refers to a diverse range of disorders that are divided into three categories: oligoarthritis, polyarthritis, and

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systemic onset diseases. According on demographic parameters, clinical aspects, treatment modalities, and disease prognosis, the disease is split into many categories. Recurrent fever and rash characterize systemic juvenile idiopathic arthritis, which is one of the most common disease subgroups.[2]

Anti-nuclear antibody positive and anterior uveitis are prevalent in oligoarticular juvenile idiopathic arthritis, which is more common in young female patients. Only around 10% of pediatric patients have seropositive polyarticular juvenile idiopathic arthritis, which is similar to adult rheumatoid arthritis. Seronegative polyarticular juvenile idiopathic arthritis is a type of idiopathic arthritis that affects both big and small joints and is more common in children. The first two types of JRA oligoarthritis, polyarthritis are classified as T helper 1 (Th1) cell-mediated inflammatory illnesses, owing to the high number of activated Th1 cells in the inflamed synovium and the pathogenetic function of Th1 cell-stimulated monocyte-produced proinflammatory cytokines. [3]

JIA treatment has evolved during the last two decades. Clinical trials research has been directed at more specific therapeutics based on what has been discovered about the biology of disease. JIA was treated before with nonsteroidal anti-inflammatory medications (NSAIDs) with delayed addition of advanced therapy; typically after cartilage damage had occurred. [4]

2. EPIDEMIOLOGY

JIA is the most common chronic rheumatic disease of childhood and a leading cause of short- and long-term disability. Its reported incidence and prevalence in European and North American populations range from 2 to 20 and from 16 to 150 per 100,000, respectively [1] In a study conducted in Turkey, Polyarticular JIA was the most common subtype in the analysis, and there were fewer individuals with positive ANA or uveitis than in other investigations. [5] Also in some studies it was noted the polyarticular JIA affects females more than males.

JIA has a different incidence and prevalence depending on location and genetics. According to studies, the incidence is 2-20 per 100,000 children, and the prevalence is 7-400 per 100,000 children and the average onset age was 8.1 years [5].

JIA is the most prevalent rheumatic disease in children, and it can cause severe pain, joint deformity, and growth problems, as well as active arthritis that lasts into adulthood. [6] Females are substantially more likely than males to be affected by practically all kinds of JIA, Involvement of the temporomandibular joint in JIA ranges from 17 to 87 percent. Limited mouth opening with developing open bite, retrognathia, microgenia, and a bird-like look are some of the symptoms. In the present example, this is the most severe form of JIA.[7] The temporomandibular joint (TMJ) remains a difficult-to-treat and common site of involvement for juvenile arthritis, impairing mandibular growth and development and potentially resulting in deformity and poor quality of life. [8]

Children in North America and Europe are more likely to contract the disease than those in Asia and Africa [5]. ERA was shown to be the most common form in Asia and the Middle East countries, despite the fact that oligoarticular JIA is the most common subtype in Europe and North America. This demonstrates the importance of both hereditary and environmental influences [9,10,11,12].

2.1 Pathogenesis

T-cells, B-cells, and activated macrophages infiltrate synovitis in people with JIA. The release of proinflammatory cytokines causes more inflammatory cells to arrive. This inflammatory soup aids in the development of pannus [13].

The functions of synovial fibroblasts, chondrocytes, and osteoclasts are altered, causing cartilage deterioration and finally bone erosion, resulting in joint injury. Classic signs of joint space loss and erosions, as well as ankylosis, growth disturbance, and joint misalignment, are visible as cartilage and articular bone are damaged [13,14,15].

2.2 Types

The main subtypes of JIA are:

- **Systemic JIA**: It is defined mostly by systemic symptoms, affects both boys and females equally, and can strike at any time during childhood. Systemic JIA accounts for 10-20% of all JIA cases. [2]
- **Polyarticular Juvenile Idiopathic Arthritis**: It is defined as arthritis that affects at least five joints in the first six months of the

disease. According on RF positive, the disease is separated into two categories, with females being more affected. [1,2,3]

- **Enthesitis Related Arthritis**: It is one of the most controversial issues among children with rheumatoid arthritis. it shows the characteristics of both JIA and juvenile spondyloarthropathies. And thus different names have been used during the past few years to describe same disease. The patients' major characteristics are RF and ANA negative, as well as enthesopathy and asymmetric arthritis of the lower extremities. [2]
- **Juvenile Psoriatic Arthritis**is characterised by arthritis, psoriasis, or two of the following symptoms: dactylitis; nail pitting or onycholysis [2]
- **Juvenile Idiopathic Arthritis and Uveitis**: The frequency of JIA-associated anterior non-granulomatous uveitis has been reported to be 15-67 percent in various European countries [2]Up to 21% of people with oligoarticular illness and 10% of patients with polyarticular disease acquire this condition. [3] making JIA associated uveitis one of the most severe extra-articular symptoms of JIA [2,3]

Oligoarticularthritis JIA is a seemingly benign variant of the disease that affects 1 to 4 joints asymmetrically, mostly in the lower limbs. The oligoarticular variant of juvenile idiopathic arthritis (o-JIA) accounts for up to 70% of all JIA cases in children aged 0–6 years [16].

2.3 Symptom and Diagnosis

According to a study Arthralgias were the most common initial presenting symptoms/complaints in (98.1%) patients, followed by (with overlapping) fever (52.1%), fatigue, malaise, morning stiffness in 33 (15.5%), and Raynaud phenomenon (0.5%). [5] Also disease status variables predict a modest to medium fraction of variance in pain ratings across studies. [17,18,19,20,21,22,23]

Some of the symptoms of the JIA differ depending of the type of disease in that context the International League of Associations for Rheumatology (ILAR) Classifies JIR into:

2.4 Systemic Arthritis

Fever lasting at least two weeks (dally for at least three days) and arthritis in 21 joints, as well as one or more of the following:

- Erythematous rash
- Generalized lymph node enlargement
- Hepatomegaly and/or splenomegaly
- Serositis [24,25]

Infectious, oncologic, autoimmune, and autoinflammatorydisease must all be ruled out before a diagnosis can be made [26].

2.5 Oligoarthritis

During the first six months of the disease, arthritis affects less than four joints.There are two types of subcategories, persistent (affecting no more than four joints over the course of the disease) and extended (after the first six months of the condition, more than four joints are affected) [24,25].

2.5.1 Polyarthritis, RF (-)

Arthritis that affects 5 or more joints in the first 6 months of the disease and a negative RF test. [24,25]

2.5.2 Polyarthritis, RF (+)

During the first six months of the disease, arthritis affects five or more joints. During the first six months of disease, two or more RF tests performed at least three months apart are positive. [24,25]

2.5.3 Psoriatic arthritis

Arthritis and psoriasis, or arthritis and at least 2 of the following:

- Dactylitis
- Nail pitting or onycholysis
- Psoriasis in a first-degree relative [24,25]

2.6 Enthesitis Related Arthritis

Arthritis and/or enthesitis, with at least 2 of following:

- Tenderness in the sacroiliac joint and/or inflammatory lumbosacral pain now or in the past
- The existence of HLA-B27 antigen
- The start of JIA in a male over 6 years of age
- Acute (symptomatic) anterior uveitis
- in a first-degree family member, who has the a History of ankylosing spondylitis, or sacroilitis with inflammatory bowel disease, enthesitis related arthritis, Reiter's syndrome, or acute anterior uveitis [24,25].

In JIA, there is no specific test for diagnosing the condition or forecasting its progression. But the most common effective methods include:

2.6.1 Laboratory

CBC, ESR, CRP, ANA, RF, anti-cyclic citrullinated peptide antibodies (anti-CCP), and HLA-B27 should all be included in the initial laboratory assays. Inflammatory indicators are frequent in oligoarthritis, particularly. When macrophage activation syndrome (MAS) is suspected, ferritin, fibrinogen, AST, and triglyceride tests are advised [27] the severity of the inflammatory condition is usually reflected in hematologic abnormalities.

In children with active disease, leukocytosis is prevalent, and their platelet count might rise in cases of severe systemic or polyarticular involvement. An anomaly in the distribution serum immunoglobulins concentrations of IgG, IgA, and IgM in JIA is also present. Immunoglobulin levels in the blood are said to be linked to disease activity and the acute phase response. [28,29,30,31]

2.6.2 Imaging

Conventional radiography are the most accessible, rapid, and cost-effective way to assess a joint. Ultrasonography is often the most effective method of detecting intra-articular fluid, especially in joints like the hip and shoulder, where fluid might be difficult to detect clinically. [28] Magnetic resonance imaging (MR imaging) is effective in detecting inflammatory changes in joints and cartilage destruction. Technetium-99m bone scans are particularly effective in detecting the early stages of inflammatory arthritis. [28] The only modality capable of objectively detecting bone marrow edema and the most sensitive in detecting bone erosions is magnetic resonance imaging (MRI) [27] [32].

3. MANAGEMENT AND TREATMENT

The Using of non-specific agents, many of which have serious side effects arebeing regarded currently as not effective with the relatively new use of biologics, more target-specific therapy that can be provided, which may be better tolerated. Continued translational research and clinical trials will help us learn more about the biology that underpins disease, with the goal of developing safer, more effective medicines and possibly a cure [6].

To reduce pain, stiffness, swelling, minimize functional handicap, and avoid joint injury, NSAIDs like Ibuprofen, Naproxen, and paracetamol, as well as Disease Modifying Anti Rheumatic Drugs (DMARDs) like Methotrexate, Sulphasalazine, and Cyclosporine, are commonly used. Patients with polyarticular arthritis who are resistant or intolerant to Methotrexate benefit from Etanercept [33].

This is a summary of the immunomodulatory pharmacological drugs that are used in JIA:

- **Nonsteroidal anti-inflammatory drugs (NSAIDs)**: basically any NSAIDs can be used to manage JIA
- **Disease modifying anti-rheumatic drugs (DMARDs)**: Leflunomide, Methotrexate, Sulfasalazine, Triple non-biologic DMARD (methotrexate, sulfasalazine, hydroxychloroquine)
- **Biologics:** Tumor necrosis factor alpha inhibitors (TNFi): [Adalimumab, Etanercept, Infliximab, Golimumab] Non-TNFi Biologics: [Abatacept (CTLA4-Ig), Tocilizumab (anti-IL-6R), Rituximab (anti-CD20)]
- **Glucocorticoids:** Oral: [Any] Intraarticular: [Triamcinolone Acetonide, Triamcinolone Hexacetonide, Methylprednisolone Acetate] [34]
- **Others:** Azathioprine, Cyclosporine, Mycophenolatemofetil, Chlorambucil [35].

Some of the treatment strategies that being used start normally with NSAIDs for 4 to 6 weeks, then move on to DMARDs, most often methotrexate, if the NSAIDs don't work. IACs are used to alleviate joint inflammation, and systemic steroids are normally taken for a brief period of time at the lowest effective dose before being discontinued after the desired response has been achieved. In the event that methotrexate fails, a trial of another DMARD or biologic therapy is started [36].

3.1 Intra-articular Steroid Injections

For active arthritis in oligoarticular JIA, glucocorticoid joint injections are frequently advised as first-line therapy or as a second-line treatment after a trial of NSAIDs [37]. It is most commonly used in oligoarticular JIA, but it can also be used in other subtypes of JIA. Researchers have discovered that taking methotrexate with it results in longer periods of remission. Other studies have shown that triamcinolone hexacetonide is more effective

than triamcinolone acetonide [4]. This treatment may require anaesthesia, especially in younger patients or when numerous joints are being injected. Subcutaneous or skin shrinkage, skin discolouration, and corticosteroid systemic effects are all possible side effects of this treatment [37,38,39,40].

3.2 Biological Treatment

Monoclonal antibodies, soluble receptors, cytokines, and cytokine antagonists are among the 'biologics,' which are huge, complex molecules produced from living organisms or synthesised using recombinant DNA technology [35].

- **The TNF inhibitors**, notably the monoclonal antibodies adalimumab and infliximab, have the biggest body of data for JIA uveitis among biologics [35].
- **Interleukin (IL)-6 inhibitors**, T-cell costimulation modulator/inhibitors, Janus kinase (JAK) inhibitors, and CD20 inhibitors are some of the other biologics that have shown promise in small case studies or current clinical trials [35]. Newer biologics, particularly interleukin-1 and interleukin-6 inhibitors, have revolutionized treatment by lowering the usage of systemic glucocorticoids [26].
- **Etanercept** is a soluble chimeric protein that combines the human TNF receptor p75 with the Fc domain of an IgG antibody. It was the first TNF inhibitor to be tested in patients with JIA. Several studies have revealed that people with JIA who take etanercept had a response rate of about 70% [37].
- **Infliximab** is a monoclonal antibody that binds to soluble as well as membrane-bound TNF. Because infliximab is not a fully humanised monoclonal antibody, it is recommended that it be used in conjunction with methotrexate to assist reduce antibody development against it [37].
- **Adalimumab**is a TNF-binding recombinant IgG monoclonal antibody that has been entirely humanised. Adalimumab with or without methotrexate was tested in polyarticular JIA patients in a randomized, double-blind, placebo-controlled experiment. all patients were given adalimumab; the ACR Pedi 30 response rate was 94 percent among patients who were also taking methotrexate [37,41].
- **Abatacept** is a soluble CTLA-4-Fc IgG fusion protein that binds to CD80/CD86 and suppresses a costimulatory signal required for T cell activation. When a TNF inhibitor fails to control polyarticular disease after four months of treatment, abatacept is indicated [37,42].
- **Anti-IL-1** therapy is one of four therapeutic options for new-onset systemic JIA. Injection site reactions and an increased risk of infection are the most common side effects of this medication class [42,43,44,45,46,47].
- Rheumatoid arthritis medication tofacitinib (CP-690,550) was approved. Tofacitinib is a Janus kinase (JAK) inhibitor that prevents several cytokines from signalling.
- **Rituximab** is a monoclonal antibody that binds to the CD20 receptor on B lymphocytes, causing them to be removed from circulation. Rituximab is prescribed for polyarticular disease that has failed to respond to TNF inhibitors and abatacept [37,42].
- **Tofacitinib**, a JAK inhibitor that prevents numerous cytokines from signalling, has demonstrated encouraging results and is now approved for the treatment of RA [48].

While TNF inhibition remains the mainstay of treatment, researchers are continuing to investigate and learn more about alternative targeted approaches, such as interleukin-6 (IL-6) blockage, inhibition of the Janus kinase (JAK) pathway, T cell activation blockade, and anti-B cell therapy [8].

Overall Patients treated with biologic modifiers have better illness outcomes and fewer problems than patients treated before the biologic era [8].

3.3 Vitamin D

Vitamin D is thought to play a role in the etiology of autoimmune illnesses as an immunological and inflammatory mediator, links between vitamin D and juvenile arthritis has been studied and aid in enhancing vitamin D status treatment in children with arthritis, and clarify vitamin D's probable role in disease etiology [49] For patients with chronic childhood arthritis, the appropriate 25(OH)D levels and dietary needs have yet to be found. In addition, the link between vitamin D level and disease activity in JIA youngsters is still unknown [49].

3.4 Physical Therapy and Sleep Intervention

Physical and occupational therapy are important aspects of JIA treatment. Splinting and foot

orthoses can help to rectify deformities and misalignments while also reducing pain. Regular physical training has been shown to improve joint discomfort and range of motion in JIA patients. When compared with healthy, children with JIA tend to have a higher incidence of poor sleep quality and sleep disruption. As part of the comprehensive management of pain in JIA, it is critical to test for and treat sleep disorders, as well as to educate patients and their families about sleep hygiene [17].

4. CONCLUSION

It is believed that genetic testing will soon allow for an earlier identification of JIA and will aid in the prediction of the disease course in children with JIA. Physicians may be able to better focus medicines by using genetic analysis. It is believed that the development of more targeted medicines will reduce overall immunosuppression as well as other side effects. Most persons with JIA can have a good quality of life if they follow current treatment options. JIA patients enjoy nearly the same quality of life as healthy peers after three years of pediatric rheumatology therapy. This is an important finding for patients and their parents' counselling. Family hardship, pain, and functional impairment were more important predictors of a substandard quality of life during the course of the research than disease activity among the factors examined at enrollment. Pediatric rheumatologists now have many more medications to offer patients, with the expectation that their disease will be managed, thanks to advances in immune system research and the introduction of biologic drugs in the twenty-first century. Continuing development in these biological agents and discoveries new drugs as long as developing current gene analysis techniques is the best method to treat JIA and provide best quality of life.

CONTENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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