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A Review on Drugs Used in the Management of Juvenile Idiopathic Arthritis

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Review Article

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Abstract

Juvenile idiopathic arthritis (JIA) is the most widespread rheumatic disease and main cause of disability in children. The disorder includes various classified forms depending on the affected joints' location and number, as well as the presence or absence of various inflammatory markers. The specific cause is not known but is believed to involve a combination of genetic, humoral, and environmental factors. The aims of treating JIA are to reduce inflammation, reach remission, alleviate pain, sustain function, and do so with minimal side effects. Nonsteroidal anti-inflammatory drugs are still beneficial in mild cases, while intra-articular steroid injections remain the most common treatment for patients with oligoarticular juvenile idiopathic arthritis. Disease-modifying drugs like methotrexate and leflunomide have shown to be effective and safe, but in numerous patients, the disease continues to be active even with this therapy. These patients are given more specific medical care like tumour necrosis factor -alpha (TNF-α) inhibitors, interleukin-1 inhibitors, interleukin-6 inhibitors, selective costimulation modulators, and selective B-cell blockade. Treatment comes with risks, as several medications necessitate monitoring and patient education to manage potential complications. If left untreated, the disease can progress and become chronic, leading to significant illness and potentially having a devastating impact on the child's quality of life. Despite the advancements in modern therapies improving patient outcomes, a significant portion of individuals still do not respond to treatment. This underscores the necessity for a deeper comprehension of disease development and recovery in order to properly categorize patients for appropriate treatment options.

Keywords: Juvenile Idiopathic Arthritis; Dmards; Biologics; TNF-A

Abbreviations: JIA: Juvenile Idiopathic Arthritis, IACs: Intra-Articular Corticosteroids, RCTs: Randomized Controlled Trials, HLA: Human Leukocyte Antigen, NSAIDS: Non-Steroidal Anti-Inflammatory Diseases.

Introduction

Juvenile idiopathic arthritis (JIA) is the most widespread rheumatic disease and the leading cause of disability in paediatric patients [1]. JIA is a chronic disease distinguished by prolonged inflammation of the synovial membrane, resulting in structural joint impairment and additional involvement of extra-articular organs. The persistent characteristic of JIA, along with its likelihood of causing irreversible complications, exerts a substantial influence on the well-being of impacted individuals and their families. Gender-based differences in prevalence exist, with girls consistently showing a higher susceptibility to JIA

compared to boys [2]. Over the previous years, there has been a significant transformation in the management of JIA marked by a shift towards early methotrexate introduction, increased utilization of intra-articular corticosteroids (IACs), and notably, the emergence of biologic disease-modifying antirheumatic drugs (DMARDs) [3]. These advancements have increased the possibility of disease remission in children with JIA. Attaining complete disease control is seen as the best therapeutic aim, as it improves the long-term prognosis [4]. Recently, new randomized controlled trials (RCTs) have expanded our knowledge on the effectiveness and safety of drug treatments for JIA, including both traditional medications and biologic DMARDs [1]. The purpose of this review is to outline the medications used to treat JIA.

The precise etiology and pathogenesis of JIA are unknown, although genetic, environmental, and autoimmune factors are believed to be influential in the disease development. There is a genetic tendency for JIA indicated by similarity rates of 25% to 40% in identical twins and siblings showing a 15- to 30-times higher likelihood of JIA compared to the general population [5]. The LACC1, LRBRA and NFIL3 genes along with human leukocyte antigen (HLA) B27, have been implicated in conferring susceptibility to the development of JIA. Environmental factors such as maternal smoking and infection may elevate the likelihood of onset or exacerbation of the disease [6]. Humoral and cellular immunity play crucial roles in the pathogenesis of JIA. The release of proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and IL-1 due to T-cell activation, is a well-documented aspect of JIA pathogenesis and remains a primary focus of numerous pharmacological interventions [7]. A prominent clinical manifestation is joint pain accompanied by morning stiffness, possibly influenced by circadian fluctuations of disease-related cytokines, notably IL-6, and compromised fibrinolysis of neutrophil-entangled fibrin deposits. Additionally, children could suffer from enthesitis, as well as lower back pain, and may also exhibit constitutional symptoms such as anorexia, loss of weight, and impaired growth. The primary extra-articular manifestation is uveitis, frequently observed in various JIA subtypes such as oligoarthritis (15.6–30%), rheumatoid factor (RF)-negative polyarthritis (4–22.5%), Psoriatic JIA (10–15%), and Enthesitis-Related Arthritis (ERA) (3–7%). The majority of JIA subtypes show persistent symptom-free inflammation in the front part of the eye (uveitis), except for ERA which usually presents as sudden symptomatic inflammation in the same area [8]. The current JIA classification system, established by the Paediatric Task Force of the International League of Associations for Rheumatology (ILAR), categorizes the disease into seven distinct groups based on clinical and laboratory findings within the initial 6 months of onset. These ILAR classifications encompass systemic (sJIA), oligoarticular, polyarticular, enthesitis-related, psoriatic (pJIA), and undifferentiated arthritis [9]. Diagnosis of JIA primarily relies on clinical symptoms and serological markers specific to each classification, emphasizing the significance of accurate subtype classification in determining prognostic indicators, outcomes, and optimal treatment strategies.

Feature	Oligoarticular	RF + Polyarticular	RF– Polyarticular	ERA	Systemic	Psoriatic
Peak age of onset	1 – 3 years	Teenage	Dual peaks	Teenage	2 years	Dual peaks
Sex	F > M	F > M	F > M	M > F *	Equal	F > M
ANA+	Majority	Rare	Majority	Rare	Rare	Majority of younger age
RF+	No	Yes	No	No	No	No
HLA-B27+	No	No	No	Majority	No	Majority of older age
Uveitis	Silent	Rare	Silent	Typically acute	Rare	Silent
Enthesitis	No	No	No	Yes	No	Older age
Dactylitis	Rare	No	No	Yes	No	Yes
Fevers	No	No	No	No	High-spiking	No

Table 1: JIA Subtypes.

By definition, children with unclassified JIA meet criteria for none or for two or more of the categories listed in the (Table 1). In older-onset psoriatic JIA, the ratio of males to females is nearly equal, and the prevalence of positive ANA

is reduced. Abbreviations: ERA– enthesitis related arthritis. Adapted from [10].

NSAID

Non-steroidal anti-inflammatory diseases (NSAIDS) have conventionally served as the primary treatment for all types of JIA. At lower doses, these medications alleviate pain through their analgesic properties, while at higher doses they exhibit anti-inflammatory effects. Within the initial 1-3 days of therapy, a reduction in pain is typically observed [11]. Nonetheless, prolonged utilization of NSAIDs as a standalone therapy for over 2 months is advised against if arthritis remains active. These drugs do not alter the course of the disease but solely address its symptoms. Only a limited number of NSAIDs have been authorized for pediatric use, with naproxen, ibuprofen, and indomethacin being the most commonly utilized [12].

Intra-Articular Injections

In the management of JIA in children, IAC injections are commonly utilized, especially in cases of oligoarthritis, to swiftly alleviate inflammatory symptoms, enhance functionality, and potentially avoid the necessity for regular systemic treatment [13]. Some paediatric rheumatologists employ a strategy involving multiple IAC injections in children with polyarticular JIA to achieve rapid resolution of synovitis, while simultaneously commencing disease-modifying antirheumatic drugs (DMARDs) and/or a biologic agent [14]. Triamcinolone hexacetonide (TH) stands as the preferred medication for JIA [15]. Although there are no established guidelines for this practice, most rheumatologists will limit the frequency of reinjections to three times per year. Adverse effects of IACs may encompass subcutaneous atrophic changes at the injection site, periarticular calcifications, crystal-induced synovitis, and the potential risk of septic arthritis. The uncertain association between IAC injections in the hip and the development of avascular necrosis of the femoral head is noteworthy [16]. Systemic corticosteroid usage primarily pertains to addressing extra-articular manifestations of systemic arthritis, such as high fever that doesn't improve with NSAIDs, severe anaemia and macrophage activation syndrome (MAS) [17]. High-dose "pulse" intravenous methylprednisolone (10–30 mg/kg/day up to 1g/day for 1–3 consecutive days) demonstrates efficacy in managing these manifestations, albeit with a short-lived impact. Thus, ongoing corticosteroid therapy with oral prednisone (1–2 mg/kg/day up to 60mg/day in single or divided daily doses) is often essential. In cases of severe polyarthritis resistant to other treatments or during the waiting period for the full therapeutic effect of a recently initiated second-line or biologic agent, a brief regimen of low-dose prednisone (e.g., 0.5 mg/kg/day) may be contemplated [1].

Non-Biologic DMARDs

The American College of Rheumatology (ACR) recommends early use of DMARDs, specifically MTX, leflunomide and/or sulfasalazine. Methotrexate (MTX) remains the most widely used conventional DMARD in the management of JIA because of its effectiveness at achieving disease control and acceptable toxic effects [18]. MTX exerts its maximum therapeutic effect with parenteral administration of 15 mg/m^2 per week and there was no additional advantage in giving higher doses up to 30 mg/m2 per week [19]. MTX can be administered via oral or subcutaneous routes, with research indicating superior effectiveness when delivered subcutaneously [20]. Adverse reactions associated with methotrexate encompass oral ulcers, nausea, and infrequently, notable hepatic enzyme irregularities. Monitoring of complete blood counts, hepatic enzymes, and renal function is advised during MTX therapy, yet the optimal frequency of assessments remains undetermined. The use of folic or folinic acid supplementation is suggested to mitigate MTX-related toxicity [21]. Certain individuals might develop a psychological resistance to methotrexate and could potentially benefit from cognitive behavioural therapy and relaxation strategies [22].

Leflunomide suppresses the production of pyrimidine, thus disrupting the proliferation of lymphocytes. Ayaz et al., demonstrated that leflunomide could offer a viable treatment option for patients who cannot tolerate MTX, and in cases of low disease activity, it may reduce the need for biologic medications. Leflunomide can serve as an alternative DMARD for psoriatic JIA when there is intolerance to MTX [23]. Side effects may consist of diarrhoea, skin rashes, cytopenia, abnormal liver function test results, and teratogenicity. A loading dose of 100 mg/day for 3 days is administered to adult-sized patients in order to achieve steady-state levels quickly due to the long half-life of the metabolite (approximately 2 weeks). Improvement can begin as early as 4 weeks after starting the medication and may continue for up to about 5 months of treatment [24].

SSZ, similar to MTX, has been a longstanding treatment for JIA. Sulfasalazine is suggested for individuals experiencing moderate ERA activity with active peripheral arthritis, but it proves ineffective in cases involving sacroiliitis [25]. It hinders the activity of enzymes and transcription factors associated with the generation of proinflammatory cytokines. Potential adverse reactions comprise nausea, vomiting, diarrhoea, loss of appetite, skin rash, bone marrow suppression, and hepatitis. Sulfasalazine's inhibition of dihydrofolate reductase may lead to folate deficiency and megaloblastic anaemias. Patients who have sensitivity to sulpha should refrain from using sulfasalazine due to the potential risk of developing Stevens–Johnson syndrome. It is recommended to regularly monitor CBC and liver enzyme levels [26].

Biologic Dmrads

The recommendations from the American College of Rheumatology advise that patients who do not show improvement with, or cannot tolerate, DMARDs are suitable candidates for biologic therapy [9]. Biological agents offer a relatively novel approach to treatment, raising high hopes for patients with JIA, especially those who do not respond to traditional treatments such as steroids and non-biological DMRADs. Biological agents used for the treatment of JIA are shown in Table 2.

Drug	Mechanism of action	Dose
Etanercept	TNF suppression, fusion protein TNF receptor suppression	0.8 mg/kg/week or two times a week 0.4 mg/kg (maximum 50 mg/week)
Infliximab	TNF suppression, anti-TNF monoclonal chimeric antibody	5-10 mg/kg/month (maximum 200 mg/month)
Adalimumab	TNF suppression, anti-TNF monoclonal antibody	30 kg: 40 mg/every 2 weeks
Anakinra	IL-1 receptor antagonist	2-10 mg/kg/day (maximum 200 mg/day)
Canakinumab	Anti IL-1b monoclonal antibody	40 kg: 150-300 mg/dose/4-8 weeks
Rilonacept	IL-1 suppression; soluble fusion protein	2.2-4.4 mg/kg/week
Tocilizumab	IL-6 receptor antagonist	30 kg: 8 mg/kg 2-4 weeks (maximum 400 mg/dose)
Abatacept	T-cell co-stimulator; soluble fusion protein	10 mg/kg/4 weeks + (maximum dose 500 mg)
Rituximab	CD20 antigen suppression	375 mg/m2/weeks, for 4 weeks (maximum dose 500 mg)

Table 2: Biological Drugs Used in Treatment of Juvenile Idiopathic Arthritis [1,9,32].

Etnercept

Etnercept, a completely human TNF inhibitor, has been approved as the initial biologic agent for JIA. This molecule attaches to soluble TNF- α, leading to a reduction in downstream TNFR-mediated signaling. Its effectiveness and safety have been well established in patients with JIA, especially those with the pJIA subtype [27]. Prince et al., utilizing the Dutch national registry for JIA patients, demonstrated that etanercept is effective and safe not just for treating pJIA patients but also for those with systemic JIA and other disease subtypes [28]. The recommended dosage is 0.8 mg/kg/week. Adverse drug reactions are infrequently documented, with mild infections and local skin reactions at the injection site being the most commonly reported non-serious events [30,29]. Out of the 95 JIA patients who were given etanercept, the main adverse effects were mild and typical injection-site reactions, with the most frequent being neuropsychiatric symptoms observed in 30 patients (23.6%).

Infliximab

Infliximab is a chimeric monoclonal antibody of the IgG1 class. In contrast to another anti-TNF agent, etanercept, which only binds to the soluble subunit, infliximab binds to both the soluble part and the membrane-bound precursor of TNF- α. This results in an interruption of the interaction between TNF-a and its receptors, leading to cell lysis in those that produce TNF- α [31]. In clinical studies, infliximab resulted in a decrease in symptoms of inflammatory conditions and induced a state of reduced disease activity in patients who did not respond to initial treatment options. The recommended dosage for the medication ranges from 3-6 mg/kg every 4-8 weeks (with a maximum dose of 200 mg). It is approved for the treatment of a number of inflammatory diseases in children, including uveitis, crohn's disease, psoriatic arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis [31,32]. In addition, patients receiving infliximab showed no increase in the occurrence of severe or opportunistic infections. However, compared to other TNF blockers, allergic responses after infliximab's intravenous (IV) administration seem to occur slightly more frequently [32,33].

Adalimumab

Adalimumab is a humanized monoclonal antibody which inhibits the interaction of TNF- α with p55 and p75 TNFRs on cell surfaces. Adalimumab is typically administered in a dose of 24 mg/m2 every 15 days (maximum 40 mg). Subcutaneous adalimumab (SC) is used to treat juvenile

rheumatoid arthritis, uveitis, and other chronic debilitating diseases caused by TNF. The use of adalimumab is safe and efficient among JIA patients. When adalimumab is used along with non-biological DMARDs (e.g., methotrexate) it become more potent [34]. The German Biologics Registry shows that adalimumab is extremely powerful in treating children and adolescents who suffer from inflammation [34,35]. It appears that adalimumab was well tolerated, effective, and safe in young children with pJIA ages 2 to 4, and those older than four with 15 kg [36]. The interim findings from the STRIVE Registry indicated that adalimumab was both well-tolerated and successful in treating most children with pJIA during the last seven years. Other important biologics databases indicated that adalimumab and infliximab had equal effectiveness in JIA patients (excluding systemic disease subtypes) after failing etanercept [37].

Anakinra

Anakinra is a recombinant human IL-1 receptor antagonist. It competes with natural ligand IL-1beta receptor type I (IL-1RI) on cell surfaces thereby blocking inflammatory responses caused by high IL-1 levels. A dose of 2-10 mg/kg/day may be given subcutaneously only (maximum 200 mg/day). Several large-scale controlled trials confirmed anakinra effectiveness in children suffering from sJIA without compromising their safety records. Dutch population-based register "National ABC" determined anakinra had better outcomes compared to TNF- α blockers among children diagnosed at young ages (<1 year) or during periods involving early puberty (puberty onset between 9-14 years old) [37].

Canakinumab

Canakinumab is a recombinant, human anti--IL-1 β monoclonal antibody. It attaches itself to human IL-1α and prevents it from interacting with IL-1Rs, therefore inhibiting its proinflammatory effects [38]. Clinical studies have shown that canakinumab can be used safely and effectively in people with SJIA. Its primary benefit over anakinra, the second anti-IL-1 treatment option, is that it only needs to be used once every month as opposed to daily injections, which are frequently poorly tolerated by paediatric patients [38]. For youngsters weighing 40 kg or less, the suggested daily dosage is 4 mg/kg every 48 weeks [31, 32]. Patients who were given a placebo had a slightly greater frequency of mild illnesses when considering their risk for infection [39].

Tocilizumab

Tocilizumab is a humanized, recombinant anti-human IL-6R monoclonal antibody. Patients with sJIA and active pJIA who do not respond to non-biological DMARDs are managed by tocilizumab. Every two to four weeks, a dose of 12 mg/kg is advised for patients weighing 12 kg.Tocilizumab has shown in several studies to be both safe and effective in treating patients with severe, ongoing sJIA and pJIA. IV injections of tocilizumab have been approved for the treatment of sJIA in patients ages two to seventeen. In a recent phase 1 open-label trial, tocilizumab treatment was examined in sJIA patients under the age of two. In sJIA patients less than two years old, the aforementioned study shown that tocilizumab at a dose of IV 12 mg/kg given every two weeks provided pharmacokinetics, pharmacodynamics, and effectiveness. With the exception of a higher frequency of significant hypersensitivity events in patients under two years old, the safety of this treatment approach was comparable [40]. Tocilizumab has been marketed for a number of years in a soft capsule form (SC), which makes the drug easier to use and improves patient outcomes. Adult RA patients have demonstrated the safety and effectiveness of SC tocilizumab in multiple clinical trials [41,42]. As far as we are aware, there are currently no reports on the effects of moving JIA patients from intravenous to subcutaneous tocilizumab. Nonetheless, there are conflicting reports about the use of SC tocilizumab in uveitis patients [43,44]. Quesada-Masachs et al. documented four patients of JIA-associated uveitis that underwent SC tocilizumab treatment following an IV medication-induced illness remission [43]. During the first several months of receiving SC tocilizumab treatment, all four subjects had a flare-up of their condition (ocular or joint) [43]. It should be remembered that because tocilizumab can alter the number of acute-phase indicators and decrease systemic characteristics of infection (fever), some infections may be underestimated and go undetected in individuals receiving this medication [32,39].

Abatacept

Abatacept is a fusion protein that is in a soluble form and has the ability to attach to the altered Fc (including the hinge, CH2, and CH3 regions) of human IgG1, along with the extracellular part of human cytotoxic T-lymphocyte-associated antigen 4. It works by inhibiting the activation of T cells and selectively modulating their co-stimulation. It is administered monthly at a dose of 10 mg/kg by injection. When non-biological DMARDs and anti-TNF medicines fail to control moderately to highly active pJIA, it is recommended as a second line therapy. SAEs in individuals on abatacept have not been reported, with the exception of minor infections [32,39].

Rituximab

Rituximab is a monoclonal antibody that is a mix of mouse and human cells and is used to target the surface of B lymphocyte. The drug is suggested to be taken three or

four times at a dose of 375 mg/m2. Currently, rituximab is recommended for use in individuals with granulomatosis with polyangiitis, microscopic polyangiitis, rheumatoid arthritis, and some non-rheumatologic diseases (such as non-Hodgkin's lymphoma). It is used off-label in paediatric patients with systemic lupus erythematosus. Studies on use of rituximab in JIA patients are very limited [45]. A study showed that rituximab was effective in patients with severe pJIA and sJIA who did not respond to previous non-biological and biological therapies [46]. It is noteworthy that a vaccination against encapsulated bacteria is required before beginning rituximab therapy [32,47].

Safety of Biologics

A few national registers and a drug-specific registry provide the majority of the information regarding the safety of etanercept [48,49]. The incidence of adverse events (AEs), serious adverse events (SAEs), medically significant infections, and autoimmune reactions were comparable amongst the 594 patients in the drug-specific registry who were treated with MTX alone, etanercept alone, and MTX and etanercept together 48. There were no documented cases of demyelinating illness, cancer, TB, or fatalities. Less encouraging data, though, have been provided by the on-going national registers. Twelve serious adverse events (SAEs) were reported in 322 patients who got etanercept (592 patient-years of exposure) in the German registry. Eleven patients had their medication discontinued permanently as a result of AEs, one of them developed thyroid cancer and the other one had demyelination. There was no evidence of an opportunistic infection or lupus-like illness [49]. A later article from the same registry [50] included five cancers out of 1260 individuals treated with etanercept. Nine SAEs and six permanent discontinuations owing to adverse events (AEs) were documented in the Dutch registry, which comprised 146 patients and 313 patient-years of exposure. There was one incidence of tuberculosis and three new-onset autoimmune disorders (sarcoidosis, Crohn's disease, and ulcerative colitis), but no demyelinating illness, opportunistic infection, cancer, or mortality [51] was observed. Out of the 483 patients in the British registry (with 941 patient-years of exposure), 21 discontinued etanercept because of adverse events: six different events, 10 central nervous system symptoms, and five infections. Agitating Bowel disease was seen in one patient, but no opportunistic infections or fatalities were noted [52]. There are fewer information available about adalimumab's safety. Twelve patients had their therapy stopped due to toxicity, and 14 patients experienced SAEs, including seven serious infections, in the registrative trial of 171 patients who took this medicine for up to 104 weeks. There were no new autoimmune disorders, TB, opportunistic infections, demyelinating diseases, cancers, or fatalities reported [53]. A randomized controlled study of infliximab revealed 26 SAEs, including six serious infections [54]. As was previously mentioned, patients treated with 3 mg/kg had a higher frequency of SAEs, infusion responses, infliximab antibodies, freshly generated ANA, and anti-DNA antibodies than patients treated with 6 mg/kg.

The administration of anti-TNF medicines has been linked to an increased risk of tuberculosis infection, which is crucial to keep in mind in clinical practice. Because of this, it is essential to do a precise TB test at the time of baseline assessment and to closely monitor the patient throughout the course of treatment [55]. It is currently unknown if anti-TNF medications have the ability to cause cancer. The US FDA announced 48 cancer cases in paediatric patients receiving TNF inhibitor treatment in 2010 [56]. However, only 19 of the 48 cases had chronic arthritis and the study was affected by a number of confounding biases, which hampered the interpretation of its findings [57]. The subsequent studies suggested that JIA itself is associated with an increased risk of malignancy and that treatment with TNF blockers does not augment this risk [58]. A more definite answer to these safety concerns will be provided by a large-scale effort aimed at collecting safety data related to biologic agents in a multinational population of children with JIA, which is underway. SAEs reported for other biologics mostly include serious non-opportunistic infections for abatacept, and reaction in the injection site and cases of hepatitis [59] for anakinra. The tolerability profile of tocilizumab has been studied in different trials over the last few years, but a pivotal role is to attribute to the TENDER and CHERISH studies for systemic JIA and polyarticular JIA, respectively [60]. The TENDER trial showed that most of the AEs during tocilizumab treatment are mild or moderate in intensity, not depending on the different dosage, and mostly represented by infections with a rate of 3.4 per patient-year with tocilizumab versus 2.9 with placebo. Streptococcal sepsis, pulmonary hypertension, neutropenia, thrombocytopenia, and high transaminases were also reported. A few years later, Yokota et al. reported two cases of MAS that may have been caused by tocilizumab, along with similar adverse events (AEs). However, more research is required to determine the precise relationship between the biologic treatment and these events [61]. In patients with sJIA, canakinumab has an excellent safety profile, according to safety data from two trials conducted by Ruperto et al. in 2012. The rate of infection during treatment was comparable to that of the placebo group. Patients did not have an increased risk of infections despite reports of transient thrombocytopenia and neutropenia [62]. Two related deaths and seven documented cases of MAS were reported. In contrast to other systemic JIA patients, the death rate did not rise.

Emerging Therapies

New medications for Juvenile Idiopathic Arthritis (JIA) are currently in the process of being created and undergoing clinical trials to enhance treatment choices. Clinical trials are currently testing the safety and potential effectiveness of tadekinig alfa (anti-IL18) and emapalumab (anti-IFNγ) for treating sJIA [63,64]. Additional biologics that show potential are sarilumab, secukinumab, and ustekinumab. Secukinumab inhibits IL-17A while ustekinumab inhibits IL-12/IL-23, targeting separate pathways in the immune system. A 2021 study in Rheumatology compared patients' characteristics who were treated with ustekinumab or secukinumab in the context of psoriatic arthritis. The research showed that secukinumab had a greater rate of drug persistence after 2 years than ustekinumab, suggesting that patients might be more inclined to keep using secukinumab [65]. Another group of biological DMARDs consists of the inhibitors of Janus-associated tyrosine kinases (JAK). Their action involves blocking JAK-STAT pathways to halt the transmission of external pro-inflammatory signals into the cell nucleus [66]. Exploration of the effectiveness of tofacitinib and baricitinib, the first generation of JAK inhibitors, began with adults suffering from RA and later extended to other autoimmune diseases like ankylosing spondylitis, SLE, inflammatory bowel disease, and psoriasis. The safety and effectiveness of tofacitinib in treating pJIA have been confirmed in a double blind, multinational phase 3 clinical trial (NCT02592434), showing a decrease in flares and disease activity [67].

Conclusion

In summary, JIA is a long-term rheumatic condition in children, distinguished by worsening joint damage and severe overall symptoms. Various types of DMARDs, including T-cell inhibitors, anti-TNFα agents, IL1 and IL6 blockers, and JAK inhibitors, have greatly enhanced the treatment of JIA. While some studies have shown the effectiveness and safety of biological agents in children, the topic of infections has continued to be widely debated in recent years. Close cooperation is essential between rheumatologists and infectious disease specialists when monitoring JIA patients undergoing biological treatment. There is no definite link between biological agents and cancer according to current literature. Nevertheless, there is a clear necessity for future, extensive studies conducted at multiple centres that can provide more compelling evidence regarding the safety of biological treatment. Despite the advancements in modern therapies improving patient outcomes, a significant portion of individuals still do not respond to treatment. This underscores the necessity for a deeper comprehension of disease development and recovery in order to properly categorize patients for appropriate treatment options.

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