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Systemic juvenile idiopathic arthritis — current diagnostic and therapeutic management

ABSTRACT

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of arthritis that has seven subtypes under the currently applicable ILAR classification. It is the most common arthropathy diagnosed in children, a chronic disease affecting children and adolescents. The systemic form of juvenile idiopathic arthritis (SJIA) is the most frequent subtype of the disease with a different aetiopathogenesis, broad clinical picture, various courses, burdened with numerous complications and requiring a therapeutic approach that is different than in other subtypes of JIA. In the case of SJIA, it is essential to establish the correct diagnosis as soon as possible and to initiate effective treatment and, if there is no effect after standard steroid therapy, use targeted anti-cytokine therapy. This review discusses current data on the aetiopathogenesis of the disease, clinical presentation and principles of diagnostic and therapeutic management.

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KEY WORDS: juvenile idiopathic arthritis; pathogenesis; cytokines; treatment

INTRODUCTION

Juvenile idiopathic arthritis is the most common inflammatory arthritis of childhood, with a heterogeneous clinical presentation, diverse prognoses and a risk of complications. According to the current classification, there are seven clinical categories of the disease. Of all the subtypes of JIA, the form with systemic onset (SJIA) is the most severe and potentially life-threatening. Typical clinical signs include high fever accompanied by a salmon-coloured rash. In addition, there is lymphadenopathy, hepato- and/or splenomegaly and serositis. In SJIA, an even ratio of girls and boys is recorded, any age of onset is possible. Laboratory findings are characterised by very high inflammatory markers, high ferritin and D-dimer levels, high levels of circulating interleukin 1, 6, 18 (IL-1, Il-6, IL-18) [1, 2].

Contemporary therapeutic management allows control of systemic inflammation and reduction of side effects associated with classical corticosteroid (GCs) treatment. In the early phase of the disease, it is reasonable to use high doses of GCs, but if symptoms persist or reducing doses of GCs is not possible after 2–4 weeks, early introduction of anti-cytokine treatment (IL-1 or IL-6 blockers) is advisable to prevent complications and side effects of steroid therapy.

AETIOPATHOGENESIS OF THE SYSTEMIC FORM OF JUVENILE IDIOPATHIC ARTHRITIS

The aspects of the pathogenesis of SJIA known so far point to important differences from other forms of the disease. **Because the pathogenesis of SJIA is based on disturbances of the innate immune system, it is classified as an autoinflammatory disease.** The role of the acquired immune response is much less significant, compared to other forms of the disease [2, 3].

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GENETIC PREDISPOSITION

Genetic studies have indicated possible associations with polymorphisms in regulatory sequences of pro-inflammatory cytokines [3]. Two genes are particularly important for susceptibility to SJIA, as confirmed by a recent study on an international population of children with SJIA: the HLA class II genes and the HDAC9 gene, which encodes histone deacetylase [4]. HLA class II molecules present peptide antigens to T-cell receptors on CD4+ T-cells, which results in their activation. HDAC9 causes important epigenetic effects through deacetylation of histone proteins and regulation of innate immune processes, including Toll-like receptor signalling and development of regulatory T-cells. Single nucleotide polymorphisms (SNPs) in 23 other genes have also been demonstrated in patients with JIA. Comparison with other forms of the disease has shown that SJIA has a unique genetic architecture, confirming the distinct pathophysiological mechanisms [4].

IMMUNE SYSTEM

The impairment of control mechanisms in innate immune cells plays an important role in the pathogenesis of SJIA. In the active phase of the disease, the number of activated monocytes/macrophages and neutrophils is increased, while the number and function of NK cells is reduced [5]. Monocytes from SJIA patients show increased activation of the NLRP3 inflammasome, resulting in increased caspase-1 activation. Caspase-1 cleaves inactive pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, which are the active forms of pro-inflammatory cytokines. The binding of IL-1β and IL-18 to their receptors activates the nuclear transcription factor NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) which regulates the expression of pro-inflammatory genes of IL-1, IL-6, TNF and IL-18 cytokines, enhancing the inflammatory phenotype in SJIA [6]. In SJIA, neutrophils and monocytes release large amounts of S100 proteins. S100A8 and S100A9 form complexes that act as substrates for the Toll-like receptors TLR2 and TLR4. TLR pathways in monocytes activate NFκB, contributing to the aforementioned expression of pro-inflammatory cytokines. Under normal conditions, IL-10, an immunomodulatory cytokine, controls NRLP3 activity. In SJIA, reduced IL-10 expression correlates with disease activity [6].

INTERLEUKIN 1

The family of IL-1 cytokines comprises the major mediators of the innate immune system. Interleukin-1 is the first cytokine identified as a potent inducer of fever and inflammation. The main sources of IL-1β are tissue macrophages, blood monocytes and dendritic cells. Interleukin-1 has the ability to induce the synthesis of potent inflammatory mediators such as cyclooxygenase type 2 (COX-2), phospholipase type 2 and inducible nitric oxide (NO) synthase, which is responsible for the production of prostaglandin E2, a platelet-activating factor. In addition, IL-1 has angiogenic properties. The IL-1 family includes seven pro-inflammatory cytokines: IL-1α, IL-1β, IL-18, IL-36α, IL-36β, IL-36γ, and IL-33) and three anti-inflammatory cytokines: IL-1Ra (blocks IL-1α and β), IL-36Ra (blocks IL-36α, β and γ, and IL-37). The function of IL-38 remains unknown [7]. The potent pro-inflammatory action of IL-1α and IL-1β is divided into three steps: synthesis and release, membrane receptor binding and intracellular signal transduction. Binding of cytokines to the receptor results in a cascade of events, including phosphorylation and ubiquitination, which results in activation of NFκB factor and AP-1-dependent expression of pro-inflammatory cytokines, chemokines and secondary inflammatory mediators [7]. Genes activated by IL-1 include IL-6, IL-8, MCP-1, COX-2, IL-1α and IL-1β. Most of the intracellular components that participate in the cellular response to IL-1 also mediate responses to other cytokines (IL-18, IL-33), TLRs and many other forms of cytotoxic stress.

INTERLEUKIN 6

Interleukin 6 acts pleiotropically in inflammatory processes, immune response and haematopoiesis. It is released by monocytes and macrophages under the influence of IL-1 and other pro-inflammatory cytokines. Under normal conditions, it is produced in response to infection or tissue damage and contributes to the body's defence by stimulating acute phase responses, haematopoiesis and immune responses. IL-6 acts on many cell types, including B and T-cells, hepatocytes, haematopoietic progenitor cells, macrophages, megakaryocytes and neuronal cells [8]. In SJIA, dysregulated, excessive IL-6 synthesis contributes to the persistence of chronic inflammation. Interleukin 6 plays an important

Table 1. Classification criteria for the systemic form of JIA (ILAR, 2001) [15, 16]

Inflammation of ≥ 1 joint, lasting at least 6 weeks with onset before 16 years of age, which presents with and/or is preceded by a high fever of at least 2 weeks duration (1–2 peaks per day) documented over 3 consecutive days, accompanied by ≥ 1 of the following symptoms: — evanescent macular or maculopapular salmon-coloured rash — generalised lymphadenopathy — hepato- and/or splenomegaly — serositis
Exclusion criteria 1. Presence or positive history of psoriasis in the patient or a first-degree relative 2. Arthritis with HLA-B27 antigen in boys > 6 years of age 3. Positive history in a first-degree relative of HLAB27 antigen presence, for AS, tendonitis-related arthritis, sacroiliac joint inflammation in the course of chronic inflammatory bowel disease, Reiter's syndrome or acute anterior uveitis Presence of rheumatoid factor (RF) (2 times in 3 months)

role in endothelial activation, enabling the recruitment of mononuclear cells at inflammatory sites, activating chronic inflammation. The release of IL-6 induces fever, leukocytosis, thrombocytosis, anaemia and the release of acute phase markers including C-reactive protein (CRP), and causes growth retardation and osteopenia [8, 9].

INTERLEUKIN 18

Interleukin 18, a member of the IL-1 family of cytokines, was originally described as an inducer of interferon-gamma (IFN-γ). It influences NK cell activity, regulates macrophage response and leads to migration, degranulation and cytokine release from neutrophils. In patients with active SJIA, serum IL-18 levels have been shown to be significantly higher than in patients with other forms of JIA, suggesting that it may be a biomarker of SJIA. Increased IL-18 production may predispose to the development of Macrophage Activation Syndrome (MAS), but the mechanisms behind this predisposing effect are still unclear [3].

DEMOGRAPHICS, DEFINITION, DIAGNOSTIC CRITERIA, CLINICAL PICTURE, COURSE OF DISEASE

The systemic form of JIA accounts for 5–40% of all cases of JIA, the prevalence of which varies in different regions of the world. In Asian countries (India, Japan) it is most common, reaching up to 30–40% of all cases of the disease. In Europe, the incidence is estimated at 5–15%, in Poland at 5–10% (in the Małopolska region — 8.8%) [10–12]. The disease can occur in any period of a child's life, but the peak incidence is between 1 and 5 years of age. Unlike other clinical categories of JIA, the generalised form occurs with equal frequency in both sexes, affecting all ethnic groups.

Table 2. The proposed new classification criteria for the systemic form of JIA (PRINTO, 2019) [17]

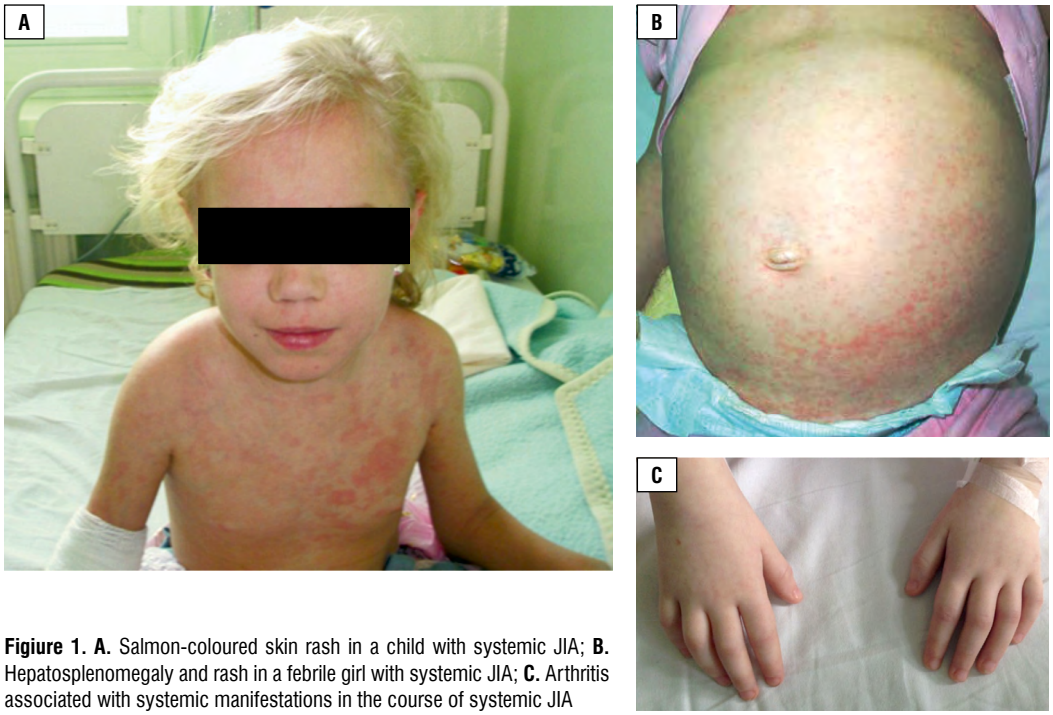
Daily fever documented for 3 consecutive days, recurrent and lasting more than 2 weeks and meeting 2 major or 1 major and 2 minor criteria. A. Major criteria 1. Evanescent rash 2. Arthritis B. Minor criteria 1. Generalized lymphadenopathy and/or hepatomegaly and/or splenomegaly 2. Serositis 3. Arthralgia lasting > 2 weeks (in the absence of arthritis) 4. Leukocytosis (> 15,000/mm^3) with neutrophilia
Exclusion criteria: known cancer, autoimmune or autoinflammatory (monogenic) diseases

By the end of the 1950s, all clinical forms of JIA were named Still's disease. Currently, the name Still's disease is assigned to the systemic form of arthritis in adults. In recent years, there has been a change in the nomenclature of Still's disease, distinguishing between juvenile onset Still's disease (JOSD) and adult onset Still's disease (AOSD) [13, 14].

CLASSIFICATION CRITERIA

Separate classification criteria still apply for patients of developmental and adult age. In the developmental age group, the ILAR criteria that define SJIA apply (Table 1).

In 2019, a new proposal of classification criteria for SJIA was published by the Paediatric Rheumatology INternational Trials Organisation (PRINTO), in which, as with AOSD, the diagnosis can be made for joint pain alone, without features of inflammation. These criteria are summarised in Table 2.



Figiure 1. A. Salmon-coloured skin rash in a child with systemic JIA; **B.** Hepatosplenomegaly and rash in a febrile girl with systemic JIA; **C.** Arthritis associated with systemic manifestations in the course of systemic JIA

Predominant systemic symptoms as in SJIA in patients over 16 years of age are defined as adult-onset Still's disease (AOSD); the Yamaguchi and Fautrel classification criteria then apply (no arthritis required, only joint pain) [14, 18, 19].

CLINICAL AND LABORATORY SIGNS

The clinical picture of SJIA, according to the definition, is dominated by prolonged fevers, lasting more than 14 days, not amenable to standard treatment, accompanied by a characteristic salmon-coloured rash and generalised lymphadenopathy, liver and/or spleen enlargement and serositis (Fig. 1A, B, C). The onset of the disease is usually sudden, the child's condition is moderate to severe, and if there are pericardial or pleural effusions, symptoms of threatening cardiopulmonary failure may occur. The generalisation of the disease process may also manifest as central nervous system (CNS) involvement, with seizures, irritation of the meninges *(meningismus*), irritability, and disturbances of consciousness. In SJIA, uveitis is rare. Increased systemic inflammation is accompanied by high inflammatory markers (ESR, CRP, hyperleukocytosis with left shift in the white blood cell count, anaemia and thrombocythemia, and hyperferritinaemia) and no RF. In addition, rare anti-nuclear antibody (ANA) pattern is typical of SJIA. The HLA-DR4 antigen is often present [20, 21].

SJIA is heterogeneous, as reflected in phenotypic variability, age of onset, differences in pro-inflammatory cytokine activity and variable response to therapy [22].

Among patients diagnosed with SJIA, at least two disease phenotypes can be distinguished:

A — with predominant systemic symptoms,

B — with predominant joint symptoms, in addition, based on a cytokine profile with high levels of IL-18, a subgroup with a higher risk of developing MAS is distinguished [23].

COURSE OF DISEASE, POOR PROGNOSIS FACTORS, COMPLICATIONS

It is estimated that approximately 40% of patients with SJIA have a monocyclic disease course with a good long-term prognosis. In a small proportion of patients, a polycyclic course is observed, with recurrent episodes of active disease and periods of remission. However, it should be noted that half of the cases of SJIA are severe, persistent form of the disease.

Factors for poor prognosis of SJIA include persisting fever, steroid dependence, thrombocytemia, polyarthritis, hip involvement and early joint damage (3–6 months from disease onset). Early predictors of joint damage and poor prognosis are young age at diagnosis (< 18 months), long disease duration, persistent use of GCs, thrombocytosis and high inflammatory parameters.

Typical complications of SJIA include early erosive arthritis, complications of steroid therapy (osteoporosis, stunting, cataract, glaucoma), cardiopulmonary complications (possible cardiac tamponade, arrhythmias, pulmonary alveolar proteinosis, interstitial lung disease, pulmonary hypertension) [20, 21, 24]. The long duration of the disease which is refractory to standard treatment has a very negative effect on growth. Observations from the times before the introduction of anti-cytokine treatment indicate that growth inhibition is observed during periods of high disease activity, with catch-up growth during periods of remission. Growth retardation is multifactorial, the primary factors being GCS treatment, secondary endocrine disorders, altered nutritional status, prolonged immobilisation and, above all, active inflammation.

In the course of SJIA, as well as in AOSD, there is the possibility of the most serious and life-threatening complication — MAS, a form of secondary lymphohistiocytosis. It affects 10–15% of patients with a full-blown clinical presentation, although subclinical forms of MAS are thought to be far more common, up to 30–40% of all SJIA cases. Key signs and symptoms indicating the development of MAS include high, unremitting fever, hepatosplenomegaly, neurological symptoms and haemorrhagic complications.

Laboratory findings include pancytopenia, increased liver enzymes (AST, ALT), lactate dehydrogenase (LDH), hypofibrinogenemia and hypertriglyceridaemia. **An important marker for monitoring the development of MAS and response to treatment is ferritin level.** The possibility of developing iatrogenic complications related to immunosuppression and new biological therapies used in SJIA (serious respiratory infections, gastroenteritis, hemiplegia, cancer) should also be highlighted [24]. In the active phase of SJIA, the levels of S100 proteins (S100A8, S100A9 and S100A12) are higher. High levels of S100A8/9 may be useful for monitoring treatment response, but their assessment is not widely available in clinical practice. Elevated levels of IL-18 and INF-γ in SJIA are a serious risk factor for the development of MAS. Further potential biomarkers are under investigation: INF-γ dependent chemokines, including the chemokine ligand CXC9 or CXCL9 [25, 26].

DIFFERENTIAL DIAGNOSIS

According to ILAR criteria, other forms of JIA should be excluded. The symptomatology of SJIA is markedly different from the other subtypes and the differential diagnosis should mainly consider disease entities with predominant systemic symptoms, including febrile conditions. In particular, generalised infection (septicaemia), severe viral and bacterial infections, neoplastic diseases (due to the clinical picture, acute lymphoblastic leukaemia (ALL) and lymphomas should be excluded, as well as systemic vasculitis (Kawasaki disease) and other inflammatory systemic connective tissue diseases (e.g. systemic lupus erythematosus, SLE) and immune disorders, including AIDS. Other autoinflammatory diseases that should be considered in the differential diagnosis are CINCA (chronic infantile neurological cutaneous articular syndrome), CAPS (cryopyrin-associated periodic syndromes), TRAPS (tumour necrosis factor receptor-associated periodic syndrome) — periodic fever associated with a defect in the receptor for tumour necrosis factor, PFAPA (periodic fever with aphthous pharyngitis adenitis) and FMV (familial mediterranean fever).

TREATMENT OF SYSTEMIC FORM OF JIA

The introduction of biological drugs in the late 1990s has significantly improved the prognosis and provided opportunities to achieve remission of the disease. Over the past two decades, the principles of treatment of SJIA have changed radically, mainly resulting in the possibility of early therapy with biological disease-modifying anti-rheumatic drugs (DMARD), mainly inhibitory to IL-1 and IL-6. At the same time, awareness and knowledge of the life-threatening complication of SJIA — secondary haemophagocytosis, MAS, has increased significantly [27]. The primary goals of treatment for SJIA include achieving and maintaining clinical remission, controlling inflammation and pain to improve function and quality of life, and discontinuing GCSs to prevent their adverse effects [28, 29].

When choosing a treatment option, the clinical presentation of the disease, the predominance of systemic symptoms or joint lesions, the severity of inflammation and the risk of MAS complications are key factors in choosing an optimal treatment option. Considering the postulated window of therapeutic opportunity,

early, targeted treatment is preferred. The biphasic model of the course of SJIA should also be considered when planning chronic therapy. After an initial period of the disease with predominantly systemic symptoms, in the absence of response to treatment, the inflammatory process moves into an adaptive phase dominated by chronic arthritis [30, 31].

The basic principles of treatment are as follows:

— it should be introduced as early as possible,
— the presence of poor prognosis factors should be taken into account,
— the choice of drugs should take into account the clinical course,
— disease activity should be taken into account,
— treatment should be modified depending on the response to the initial therapy,
— and it should be comprehensive (rehabilitation, psychological care, etc. should be included) [33].

Clinical trials and numerous reports on the use of IL-1 and Il-6 inhibitors (anakinra, canakinumab, rilonacept and tocilizumab) for the treatment of SJIA provide reliable evidence of both efficacy and safety. Before the times of anti-cytokine drugs, many patients with SJIA were treated chronically with GCs, sometimes even for many years, which resulted in a number of side effects, including stunted growth, osteoporosis, post-steroid diabetes or obesity. The standardised CARRA study presents consensus treatment plans for SJIA, as do the German guidelines [31, 32].

Classical DMARDs are not recommended in SJIA for use as monotherapy in early disease and with persistent systemic symptoms. However, they are recommended in combination with bDMARDs in patients with arthritis. **GCs are effective in the treatment of the initial phase of SJIA and are commonly used in monotherapy in the form of methylprednisolone pulses (dosage 10–30 mg/kg body weight). Early use of IL-1 or IL-6 blockers is currently recommended, with the aim of reducing GCs doses or discontinuing GCs altogether [31, 33].**

Currently, the treatment of SJIA, as with other forms, is based on the treat-to--target (T2T) strategy, whereby the goal of treatment is to achieve remission; where this is not possible, an alternative treatment goal is to achieve low disease activity. In 2013, updated treatment recommendations for SJIA were published by the American College of Rheumatology (ACR) [34]. They were followed by Polish recommendations, but the dynamic development of knowledge concerning the pathogenesis of this form of the disease and the emergence of new forms of biological therapies approved for the treatment of this form of the disease requires them to be updated regularly [35]. In 2018, the German Society for Paediatric Rheumatology (GKJR) defined diagnostic and therapeutic strategies for SJIA. The project was initiated in 2015. Based on a systematic literature review and analysis of data from three national registries in Germany, a consensus was developed for the diagnosis and management of SJIA [31]. **The overarching goal of SJIA treatment is: to achieve clinically inactive disease (preferably without GCs) and, ultimately, clinical remission.**

The intermediate objectives are:

— within **7 days** from the commencement of treatment:
  • resolution of fever,
  • a reduction in CRP levels by at least 50%;
— within **4 weeks:**
  • improvement in the physician's global assessment of disease activity (PGA) score by at least 50% and reduction in the number of joints with active arthritis (if any) by at least 50%
  • **or** JADAS-10 score of maximum 5.4.

The treatment strategy is based on a treatment regimen that includes:

— initial treatment, which includes the options of GCs, anakinra, canakinumab or tocilizumab;
— systemic or intra-articular CSs, non-steroidal anti-inflammatory drugs (NSAIDs) and/or methotrexate (MTX) can be used as an adjunct to biologics;
— patients with persistent polyarthritis without systemic inflammation can be treated with TNF inhibitors or abatacept.

IL-1 INHIBITORS

Anakinra (recombinant IL-1R antagonist) and canakinumab (fully human IgG1 class monoclonal antibody against IL-1) are commonly used to inhibit IL-1 in SJIA. Three anti-IL-1 drugs are available in Europe and the US: anakinra, canakinumab and rilonacept (soluble receptor fusion protein, blocks IL-1α and IL-1β). Two of them, anakinra and canakinumab, are approved for clinical use in Europe and the US, while

rilonacept is only approved in the US. The first step to initiate an inflammatory response is the binding of interleukin 1 to the type 1 IL-1 receptor (IL-1R1) and the adaptor protein IL-1RAcP to trigger signal transduction. Anakinra, a recombinant human IL-1R1 antagonist, directly competes with IL-1 for binding to IL-1R1, blocking the biological activity of IL-1, both IL-1α and IL-1β belonging to the IL-1 family. In contrast, canakinumab selectively neutralises IL-1β and inhibits its binding to IL-1R.

Kanakinumab and anakinra differ in their duration of action, which affects their dosing regimen. For anakinra, these are daily subcutaneous injections at a dose of 1mg/kg body weight (half-life 4 hours), while for canakinumab, a dose of 4 mg/kg body weight subcutaneously every 4 weeks (half-life 21–28 days) is required.

Anakinra is preferred as an initial treatment or used in the early stages of the disease. **Potential predictors of a good response to anakinra include higher ferritin levels, the predominance of systemic symptoms, high leukocytosis with neutrophilia and older age at onset** [36]. Homozygous IL-1 receptor antagonist alleles have been identified as a potential genetic marker for lack of response to anakinra; in this case, another therapy should be considered [37]. **Canakinumab is characterised by a rapid onset of action — as early as day 3 after administration — on systemic symptoms, with a significant reduction in fever compared to baseline, as well as a reduction in physician global assessment (PGA) values and CRP levels.** On the third day after administration, 100% of patients in the canakinumab treatment group, compared with 86.8% in the placebo group, had a normal body temperature ($p = 0.0098$) [38]. Shorter disease duration and lack of prior use of other biological DMARDs (bDMARDs) are associated with achieving long-term remission after canakinumab [39]. Achieving ACR improvement within 50 to 15 days of canakinumab, with the complete withdrawal of GCs, was a predictor of achieving long-term clinical remission [40]. The good response to canakinumab has been shown to be associated with high counts of neutrophils and IL-1-related genes, as well as higher IL-18 to CXCL-9 and INFγ to CXCL9 ratios at disease onset, whereas increased CD163 expression was associated with a lack of response to the drug [39, 41, 42].

IL-6 INHIBITORS

Tocilizumab (a humanised IgG1 monoclonal antibody that binds to the IL-6 receptor) is an effective and safe drug with a very broad application in the treatment of SJIA. **Currently, in Poland, tocilizumab is widely used in the treatment of SJIA as there is no other available biological treatment option for this indication**. In the German autoinflammatory disease registry, a total of 46/200 patients with SJIA received tocilizumab, of which nearly half (46%, 21/46) received it as their first biologic drug. Of these, 67% of patients (14/21) achieved inactive disease status or clinical remission on medication after one year of therapy [43–45].

OTHER TREATMENT OPTIONS FOR REFRACTORY SJIA

Currently, the first-line treatment of SJIA is GCS and increasingly, interchangeably IL-1 and IL-6 inhibitors, but in practice, there are still cases where this treatment is not effective. In this situation, with persistently high disease activity, there are descriptions of treatment with other bDMARDs, mainly TNF inhibitors and anti-CD20 drugs (rituximab) or multidrug combinations of bDMARDs, but without a satisfactory effect of such therapies. The recent FDA approval of tofacitinib for treatment of patients diagnosed with multijoint JIA is a hopeful fact for the future; however, it should be mentioned that the ongoing clinical trial using this drug in SJIA has not yet been completed. However, it can be expected that Janus kinase inhibitors (JAKs) may prove to be a viable new therapeutic option for treatment-resistant SJIA [10, 46, 47].

In SJIA with predominant joint symptoms, depending on the number of joints involved, the same drugs are recommended as in polyarthritis (pJIA) or oligoarthritis (oJIA), i.e. NSAIDs (in children with low disease activity) and intra-articular GCs and MTX. For patients whose disease activity is high despite this treatment, ACR recommends abatacept (recombinant soluble fusion protein that blocks CD80 and CD86 molecules) but this drug is not registered in Poland for the treatment of JIA [48].

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