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Recommendations for the therapeutic management of systemic juvenile idiopathic arthritis

Opinion of the Section of Developmental Age Rheumatology of the Polish Society of Rheumatology

ABSTRACT

Advances in paediatric rheumatology determine the need to update management rules and implement the latest treatment standards for patients under our care. The following case provides the current therapeutic management of patients with systemic juvenile idiopathic arthritis (SJIA), taking into consideration the Treat to Target (T2T) concept, i.e. therapy aimed at achieving remission or, when this is not possible, an alternative goal is low disease activity. Simultaneously, the authors refer to the possibility of implementing these recommendations in Polish conditions, taking into consideration the B.33 drug programme, and they highlight that therapeutic options in SJIA should include both the individual course of the disease and available treatment options in the current legal and organisational system in Poland. In the early stages of the disease, nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids (GCs) are used for managing systemic symptoms of the disease. Advances in knowledge regarding the pathogenesis of SJIA have meant that current therapeutic strategies for the treatment of SJIA are based on targeted approaches using anti-cytokine therapy that inhibits the activity of pro-inflammatory cytokines, primarily IL-1 and IL-6, and thus it is necessary to include IL-1 or IL-6 inhibitors in treatment when NSAIDs and GCs are not effective. It is considered necessary to include IL-1 inhibitors in the B.33 programme, primarily because of its causal effect. IL-1 is a mediator of the innate immune system and is a potent inducer of fever and inflammation. IL-1 inhibitors (iIL-1) enable GC-sparing effects with a reduction in their side effects. The overall response rate to IL-1 blockers (anakinra and canakinumab) is high, up to 90%, especially in patients with treatment-resistant forms of SJIA.

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INTRODUCTION

In terms of all the clinical categories of JIA, JIA with generalised onset (systemic, SJIA) is the most severe and potentially life-threatening form of disease. The clinical picture is dominated by refractory hectic fever, a characteristic salmon-coloured rash, lymphadenopathy, hepatosplenomegaly and serositis. Compared to the other subtypes of JIA, JIA with systemic onset is considered to be an autoinflammatory disease and the good response to cytokine blocking therapy reveals a key pathogenetic role of cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6). Modern therapeutic management enables systemic inflammation to be controlled and side effects associated with standard GC treatment to be reduced. In light of current knowledge, it is reasonable to use high doses of GCs in the early stage of the disease. However, if symptoms persist or it is not possible to reduce doses of GCSs after 2–4 weeks, it is advisable to implement early anti-cytokine therapy to prevent complications and side effects of steroid therapy.

DEMOGRAPHIC DATA, DEFINITION, CLINICAL PICTURE, COURSE OF THE DISEASE AND COMPLICATIONS OF SJIA

Systemic JIA makes up 5–20% of all cases of JIA. In Asian countries (India, Japan), it reaches up to 30–40% of all cases [1–4]. The disease can occur at any time in a child's life, with a peak in incidence between the ages of 1 and 5. Unlike other categories of JIA, systemic-onset JIA occurs with equal frequency in girls and boys and affects all ethnic groups.

According to recent trends (PRINTO criteria), SJIA is referred to as juvenile-onset Still disease (JOSD) [5]. Patients older than 16 years, who present with dominant systemic symptoms as in SJIA, are defined as patients with adult-onset Still's disease (AOSD); Yamaguchi and Fautrel classification criteria then apply — no signs of arthritis required, only joint pain [6, 7].

CRITERIA FOR THE DIAGNOSIS OF SJIA (ILAR 1997/2001)

The criteria for the diagnosis of SJIA according to International League of Associations of Rheumatology (ILAR) are shown in Table 1. The ILAR definition identifies SJIA as inflammation of at least one joint that lasts at least 6 weeks. Its onset is before the age of 16 and is accompanied/preceded by a high fever lasting at least 2 weeks (1–2 temperature peaks per day) that has a documented history of 3 consecutive days, which is accompanied by at least one of the following symptoms: rash, lymphadenopathy, hepatomegaly and/or splenomegaly and serositis [1].

CRITERIA FOR THE DIAGNOSIS OF SJIA (PRINTO 2019)

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

Less common manifestations of SJIA include central nervous system (CNS) symptoms such as convulsions, *meningismus*, irritation and disturbance of consciousness. Uveitis is rare. Increased clinical symptoms are accompanied by high inflammatory markers and abnormalities in laboratory tests, ESR, CRP, hyperferritinemia, hyperleukocytosis with rejuvenation of the differential blood count, anaemia and thrombocythemia [8, 9].

It is estimated that approximately 40% of SJIA patients 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 a severe, persistent form of the disease. Factors for poor prognosis in SJIA include persistent fever, steroid dependence, thrombocythemia, polyarthritis, hip involvement and early joint damage — 3–6 months from disease onset. In the course of SJIA there is a possibility of numerous complications, the most serious and life-threatening of which is macrophage activation syndrome (MAS). MAS affects 10–15% of patients, although its subclinical forms are thought to be far more common, up to 30–40% of all SJIA cases [10–12]. Key signs and symptoms that indicate the development of MAS include high, unremitting fever, hepatosplenomegaly, neurological symptoms and haemorrhagic complications. Laboratory findings include pancytopenia, elevated liver enzymes (AspAT, ALAT), lactate dehydrogenase (LDH), hypofibrinogenemia and

Table 1. Criteria for the diagnosis of SJIA (ILAR 1997/2001)

I	Inflammation of one or more joints
II	Documented fever of at least two weeks duration (including three consecutive days)
III	Presence of one or more of the following symptoms:
A	rash, evanescent macular or maculopapular salmon-coloured rash
B	hepatomegaly and/or splenomegaly
C	generalised lymphadenopathy
D	serositis (pericardial, pleural, peritoneal effusions)

SJIA — systemic juvenile idiopathic arthritis; ILAR — International League of Associations of Rheumatology

Table 2. Suggested new classification criteria for SJIA (PRINTO 2019)

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. Generalised lymphadenopathy and/or hepatomegaly and/or splenomegaly 2. Serositis 3. Joint pain > 2 weeks (if there is no arthritis) 4. Leukocytosis (> 15,000/mm^3) with neutrophilia
Exclusion criteria: known cancer, autoimmune or autoinflammatory (monogenic) diseases

SJIA — systemic juvenile idiopathic arthritis; PRINTO — Paediatric Rheumatology INternational Trials Organisation

hypertriglyceridaemia. An important marker for monitoring the development of MAS and response to treatment is ferritin level. 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), amyloidosis.

A major problem is the possibility of developing iatrogenic complications related to immunosuppression and new biological therapies used in SJIA, especially serious respiratory infections, gastroenteritis, shingles and cancer [11–13].

ETIOPATHOGENESIS OF SYSTEMIC-ONSET JIA

Systemic juvenile idiopathic arthritis is classified as an autoinflammatory disease, in the pathogenesis of which disorders of innate immune mechanisms play a major role. The role of the adaptive immune response is much reduced compared to other forms of the disease. The autoinflammatory etiopathogenesis of SJIA is confirmed by rare occurrence of antigen-specific autoreactive T and B lymphocytes, with an increased number of immature neutrophils and immature myelomonocytoid progenitor cells in the active phase of the disease. Innate immunity gene disorders result in the development of autoinflammatory diseases with consequent suppression of natural killer (NK) cell and T cell gene expression as well as biological processes associated with MHC class II and impaired antigen presentation.

Impaired control mechanisms in cells of the innate immune system play 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. In SJIA, overactivation of IL-1-, IL-6- and IL-18-related innate immunity genes and peroxisome proliferator-activated receptor gamma is observed. IL-1 has the ability to induce the synthesis of primary inflammatory mediators; the IL-1 family of cytokines comprises major mediators of the innate immune system. IL-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.

In SJIA, dysregulated, excessive IL-6 synthesis has a pathological effect on the persistence of chronic inflammation. IL-6 plays an important role in endothelial activation by enabling the recruitment of mononuclear cells at inflammatory sites and activating chronic inflammation. The release of IL-6 induces fever, leukocytosis, thrombocytosis (thrombocythemia), anaemia and the release of acute-phase markers, including C-reactive protein (CRP), and causes growth retardation and osteopenia.

Serum IL-18 levels are significantly elevated in patients with active SJIA compared to 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 MAS [14–17].

TREATMENT OF SYSTEMIC-ONSET JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

The treatment of SJIA is always a major challenge for paediatric rheumatologists,

Table 3. Dose, route of administration and intervals of IL-1 blockers in the treatment of SJIA

Biological drug	Canakinumab	Anakinra	Rilonacept***
Mechanism of action	Monoclonal Ab, blocks IL-1β	Recombinant IL-1R antagonist, blocks IL-1α and IL-1β	Soluble receptor fusion protein, blocks IL-1α and IL-1β
Dose per kg body weight	2–4 mg*	1 mg	An initial dose of 4.4 mg followed by 2.2 mg**
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous
Frequency	Every 4 weeks	Every day	Weekly

*For patients ≥ 15 and ≤ 40 kg — 2 mg/kg body weight; for patients ≥ 7.5 and < 15 kg — 4 mg/kg body weight. **Maximum loading dose 320 mg, maximum weekly dose 160 mg. ***Not registered in the European Union

although in the era of biologic drugs, the achievement of remission of the disease is much more feasible than in the late 1990s.

The essential goals of SJIA treatment include:

A. Achievement and persistence of clinical remission,
B. Control of inflammation and pain to improve function and quality of life,
C. Maximising the duration of GC administration to reduce long-term systemic complications.

Currently, the treatment principles of SJIA, like other clinical categories of SJIA, are based on a T2T strategy. The treatment aims to achieve remission. In cases 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) [18]. Based on ACR recommendations, Polish recommendations were published in 2013. However, the dynamic development of knowledge regarding the pathogenesis of this form of the disease and the emergence of new types of biological therapies approved for the treatment of this form of the disease require these recommendations to be updated regularly [19].

Standard disease-modifying antirheumatic drugs (DMARDs) are not recommended for use as monotherapy in SJIA in the early stages of the disease, or in the course of the disease with persistent systemic symptoms. Standard DMARDs are used combined with biological DMARDs in cases of arthritis. GCs are effective in the treatment of the initial phase of SJIA and they are commonly used in monotherapy in the form of methylprednisolone (Solu-Medrol) pulses (10–30 mg/kg body weight, max 1.0 g/infusion). Currently, the early use of IL-1 or IL-6 blockers is recommended, which enables dose reduction or complete withdrawal of GCs. Clinical trials and numerous reports on the use of IL-1 and IL-6 inhibitors (anakinra, canakinumab, rilonacept and tocilizumab) in the treatment of SJIA provide reliable evidence of both the efficacy and safety of these drugs that have revolutionised the treatment of SJIA [20–25].

IL-1 INHIBITORS

Anakinra and canakinumab are commonly used for inhibiting IL-1 activity. Three IL-1 blocking drugs are available in Europe and the US: anakinra, canakinumab and rilonacept. Two of them, anakinra and canakinumab, are approved for clinical use in Europe and the US, while rilonacept is only approved in the US. In the European Union, two drugs are approved for the treatment of SJIA: canakinumab and anakinra. IL-1 blocking drugs are summarised in Table 3.

Canakinumab and anakinra differ in their duration of action, which affects their dosing regimens. For anakinra, it is daily subcutaneous injections (half-life 4 hours), while canakinumab is administered every 4 weeks (half-life 21–28 days).

The recommended dose of Ilaris in patients with Still's disease (AOSD or SJIA) weighing 7.5–15 kg is 4 mg/kg body weight, above 15 kg — 2 mg/kg body weight (maximum 300 mg). A single dose of Ilaris is injected subcutaneously every 4 weeks. Longer intervals between doses of canakinumab, compared with anakinra, may have a beneficial effect on *compliance* and are more convenient for patients [26–29].

IL-6 INHIBITORS

Tocilizumab is an effective and safe drug with a very wide application in the treatment of SJIA, it is highly effective, rapid response to treatment, resolution of fever and organ symptoms as well as improvement in general condition and normalisation of inflammatory markers is observed [24, 30–33]. In the Polish

Table 4. Dosage of tocilizumab in SJIA depending on body weight

Drug name	Dosage
Tocilizumab	i.v.: < 30 kg — 12 mg/kg body weight/every 2 weeks > 30 kg — 8 mg/kg body weight/every 2 weeks

setting, tocilizumab has been widely used for 10 years in the SJIA indication; there is currently no other widely available biologic drug therapeutic option for this indication [9]. The dosage of tocilizumab is shown in Table 4.

OTHER THERAPEUTIC OPTIONS FOR THE TREATMENT OF REFRACTORY SYSTEMIC FORM OF JIA

In the case of persistently high activity of disease refractory to treatment with IL-1 and IL-6 inhibitors, attempts at treatment with other bDMARDs, mainly TNF inhibitors and anti-CD20 drugs (rituximab) or multidrug combination bDMARD therapies have been described, but optimal control of the course and of the high activity of the disease has not been achieved. The recent FDA approval of tofacitinib (inhibitor of Janus kinase, JAK) for treatment in patients diagnosed with SJIA is a promising new therapeutic option but it should be mentioned that the clinical trial using this drug in SJIA has not yet been completed [34–35].

CURRENT PROVISIONS OF THE DRUG PROGRAMME FOR THE TREATMENT OF SJIA (B.33. 2021) [36]

The current provisions of the B.33 programme for the treatment of SJIA are quoted below:

— Patients eligible for treatment with IL-6 inhibitor — tocilizumab are patients aged 2 years and older with a diagnosis of:
  - Systemic-onset JIA (diagnosis based on the 1997 ILAR criteria) with predominant systemic manifestations who, despite full doses of GCs for at least 2 weeks (oral 1–2 mg/kg/day, maximum 60 mg/day or methylprednisolone 10–30 mg/kg/day/infusions for 3 days and possibly repeated in subsequent weeks), have a fever that persists or relapses and have persisting systemic symptoms of high disease activity, defined as a value of 5 or more in a 10-point scale, as assessed by a physician or
  - Systemic-onset JIA (diagnosis based on 1997 ILAR criteria) with involvement of at least 5 joints or with involvement of at least 2 joints and concomitant fever above 38oC, whose active disease has persisted for at least 3 months and is insufficiently responsive to treatment with GCs at a dose of no less than 0.5 mg/kg body weight/day and either methotrexate (MTX) (possibly subcutaneous) at the current dose administered for at least 3 months or, in case of MTX intolerance, another disease-modifying/immunosuppressive drug administered at the current dose for at least 3 months.

— Also, patients treated for JIA with a TNF-alpha inhibitor or tocilizumab under the drug programme are eligible if they:
  - developed a severe allergic reaction to an active substance or an excipient, or
  - suffered from serious side effects that make it impossible to continue treatment and which do not subside with dose adjustments according to the SmPC, or
  - showed a lack or loss of response to the treatment applied (as defined in the exclusion criteria in the section on JIA of this drug programme).

— Patients previously treated with tocilizumab in hospital according to diagnosis-related groups (DRG) are also eligible for the programme, provided that before the start of therapy they meet the programme inclusion criteria and do not meet the programme discontinuation criteria — after the approval of the Coordination Team for Biological Treatment in Rheumatic Diseases.

OPINION OF POLISH EXPERTS ON THERAPEUTIC MANAGEMENT OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

The use of anti-cytokine drugs has significantly modified the approach to treating SJIA; both IL-1 and IL-6 blockers are effective in treating this form of the disease. In Poland, according to the B.33 programme for the treatment of RA and JIA, it is possible to include an IL-6 blocker (tocilizumab) in the treatment 2 weeks after diagnosis. There is currently no option to include treatment with an IL-1 inhibitor.

On the basis of the presented provisions of the B.33 programme for the treatment of RA and JIA, it can be concluded that there are too few drugs in the SJIA indication. It seems necessary to include IL-1 inhibitors in the

B.33 programme, primarily because of their aetiological effect. The use of IL-1 blockers is currently recommended in SJIA patients with persistent systemic symptoms of the disease that are refractory to GCs treatment. The possibility of both primary and secondary resistance to the only available biological drug for the treatment of SJIA, which is an IL-6 blocker (tocilizumab), should also be considered. In addition, there is a possibility of side effects and allergic reactions to the drug used during the treatment. In such cases, alternative therapeutic options are not available [21–23].

In SJIA with predominant joint manifestations, depending on the number of joints involved, the same management is recommended as in the polyarticular or oligoarticular form of JIA. NSAIDs can be used in patients with low disease activity and a good prognosis. Concomitant administration of GCs is recommended. In this group of patients, the inclusion of MTX is recommended, usually 6 weeks after the onset of the disease. If moderate or high disease activity persists after three months of MTX treatment, the inclusion of TNF-α inhibitors is recommended. ACR recommends abatacept in patients with persistently high disease activity despite this treatment, but this drug is not registered in Poland for the treatment of JIA [35, 37].

SUMMARY AND REFERENCE TO POLISH CONDITIONS

The presented opinion statement represents the current principles of therapeutic management in SJIA, pointing out the existing deficiencies in this regard in Poland. The treatment of SJIA is included in the B.33 programme for the treatment of RA and JIA, implemented by the National Health Fund (NHF) [36]. Current Polish recommendations, including the B.33 programme for the treatment of children and adolescents diagnosed with SJIA, are based on the 2013 ACR recommendations. Many elements of the Polish programme comply with global guidelines and standards of management, but its main shortcoming is only partial accessibility of therapeutic options commonly used in the rest of the world. The impossibility to include IL-1 blockers, including canakinumab, significantly limits the contemporary principles of treating SJIA according to the T2T concept. There are also no options of treatment with abatacept and JAK/STAT inhibitors, which are slowly becoming another therapeutic option available in many countries.

An advantage of the Polish standards of treatment of SJIA is the possibility of rapid inclusion in the treatment (after 14 days), in the case of severe course of the disease, of IL-6 inhibitor which in many cases was the cause of outstanding improvement of our patients. The disproportion between Poland and other European Union countries in terms of the availability of various therapeutic methods is becoming even more pronounced; the delay in the availability of therapy, which exceeds 10 years, is difficult to explain to children suffering from the disease and their families. It becomes necessary to increase the availability of new therapeutic options for the treatment of SJIA, and the possibility of using IL-1 blockers (anakinra, canakinumab) in the first place seems to be a necessary condition.

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