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REVIEW ARTICLE

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Current indications for the use of Janus kinase inhibitors in the treatment of juvenile idiopathic arthritis

ABSTRACT

Juvenile idiopathic arthritis (JIA) is a group of heterogeneous conditions whose main manifestation is arthritis of unknown cause and onset in childhood or adolescence. According to current guidelines, patients with a more severe disease course are treated with conventional synthetic and biological disease-modifying antirheumatic drugs (DMARDs), which significantly improve the long-term sequelae of the disease. However, despite therapeutic advances, many patients still do not achieve an adequate response to therapy.

Janus kinase (JAK) inhibitors are a new group of targeted synthetic DMARDs previously used in adult patients to treat rheumatoid arthritis (RA). Studies on the efficacy and safety of this group of medicines in various subtypes of JIA and other rheumatic diseases in children are under way. Based on clinical trial results to date, two JAK inhibitors, tofacitinib and baricitinib, have been approved to treat selected subtypes of JIA. This article presents the current knowledge on the efficacy and safety of JIA treatment with JAK inhibitors and recommendations for their use in JIA.

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KEY WORDS: JIA; treatment; JAK inhibitors

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a group of heterogeneous conditions whose main manifestation is arthritis of unknown cause and onset in childhood or adolescence [1]. According to current guidelines, patients with a more severe disease course are treated with conventional synthetic and biological disease-modifying antirheumatic drugs (DMARDs), which have significantly improved the long-term sequelae of the disease over the past three decades [2–4]. However, despite therapeutic advances, many patients still do not achieve an adequate response to treatment. According to data from the US Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, despite the sequential use of two or more biological DMARDs, up to 45–52% of patients still have active disease [5].

Janus kinase (JAK) inhibitors are a new group of targeted synthetic DMARDs used for several years to treat rheumatoid arthritis (RA) in adults. Studies on the efficacy and safety of this group of medicines in various subtypes of JIA and other rheumatic diseases in children are under way [6, 7]. Based on the clinical trial results to date, the European Medicines Agency (EMA) approved tofacitinib in 2021 for use in treating selected subtypes of JIA. The next drug in this group, baricitinib, received approval for the treatment of selected subtypes of JIA in 2023 [8, 9].

While biological DMARDs affect extracellular components of the pathogenetic pathway in JIA, JAK inhibitors target intracellular components, so these drugs have a novel, different mechanism of action [6, 7]. In the case of persistent active disease refractory to conventional and biological DMARDs, a new group of targeted synthetic DMARDs — JAK

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inhibitors—represents a promising new treatment option for JIA.

This article presents the current knowledge on the efficacy and safety of JIA treatment with JAK inhibitors and recommendations for their use in JIA patients.

JUVENILE IDIOPATHIC ARTHRITIS

JIA is a heterogeneous group of arthritis of unknown aetiology. It persists for at least six weeks and has an onset of symptoms under the age of 16.

According to the current classification developed by the International League of Associations for Rheumatology (ILAR) expert group, it has seven subtypes. Depending on the number of joints involved, the presence of other symptoms, including systemic symptoms, and the presence or absence of rheumatoid factor (RF), ILAR identifies the following subtypes of this disease:

— oligoarthritis (persistent or extended);
— RF-positive polyarthritis;
— RF-negative polyarthritis;
— systemic;
— juvenile psoriatic arthritis (JPsA);
— enthesitis-related arthritis (ERA);
— undifferentiated arthritis [1].

EPIDEMIOLOGY AND PATHOGENESIS

JIA is the most common rheumatic disease of developmental age. Its incidence]is estimated at an average of 20 cases/100,000 population [10], while in Poland, the rate of 10/100,000 children is commonly accepted. The incidence of individual disease subtypes also varies according to world region and population. In Europe, oligoarticular JIA is the most common. The underlying causes and the exact pathomechanism are still unclear. Environmental factors such as infections, frequent exposure to antibiotics, vitamin D deficiency, stress or trauma are likely to influence the development of the disease. Gastrointestinal infections lead to a loss of diversity in the gut microbiome and disrupt tryptophan metabolism, increasing the risk of developing ERA [10–12].

There are numerous studies on the genetic determinants of JIA related to human leucocyte antigen (HLA) and non-HLA genes. The primary gene associated with ERA is HLA-B27, also found in patients diagnosed with late-onset JPsA. Genetic predisposition associated with genes other than HLA plays a key role in the onset of the inflammatory response, resulting in tissue damage. These include genes encoding the cytokines, tumour necrosis factor (TNF), interleukins (IL), such as IL-2, IL-10, IL-6, and macrophage migration inhibitory factor (MIF). Polymorphisms of the endoplasmic reticulum resident aminopeptidases 1 and 2 (ERAP1 and ERAP2) genes predispose to the development of ERA, while genes encoding cytokines IL-1, IL-6, IL-10, and MIF increase the risk of developing systemic JIA [11, 12].

Due to its heterogeneity, the pathogenesis of JIA is multifactorial and differs between subtypes. The onset of the cascade of pathophysiological events is initiated by excessive activation of T cells, B cells, natural killer (NK) cells, dendritic cells, macrophages and neutrophils with increased production of inflammatory mediators, which are responsible for joint damage and systemic complications. Oligoarticular and polyarticular JIA are characterised by activation of autoreactive, antigen-specific T cells and high titres of autoantibodies. This indicates an association with HLA class II antigens, suggesting a predominant involvement of the acquired immune response in the pathogenetic processes. However, high concentrations of cytokines released by activated monocytes and macrophages, the presence of activated neutrophils and monocytes, and macrophages with reduced capacity for phagocytosis in the synovial fluid of patients with oligoarticular JIA also confirm the important role of the innate immune response. ERA pathogenesis involves the HLA-B27 antigen presenting arthritogenic peptides to T cells, which release IL-23 and IL-17 upon activation. Early-onset JPsA is characterised by the involvement of an acquired immune response and the development of dactylitis (“sausage digit”). In contrast to the pathogenetic mechanisms described above in non-systemic JIA, which are autoimmune, an autoinflammatory pathomechanism has been demonstrated in systemic JIA. Uncontrolled activation of the innate immune response stimulates monocytes, macrophages, and neutrophils and releases large amounts of pro-inflammatory cytokines (IL-1, IL-6, IL-18), as well as specific S100 proteins (markers of phagocytic cell activation) [10–12].

This diverse pathogenesis also points to the need for a variety of drugs that effectively

inhibit inflammation with the least risk of adverse events.

CHARACTERISTICS OF JIA SUBTYPES

The main symptom of JIA is arthritis, which is clinically defined as swelling, increased warmth, pain or reduced mobility. Morning stiffness is typical; its duration indicates the severity of the inflammation. Limping may be observed in children with lower limb joint involvement [12].

OLIGOARTICULAR SUBTYPE

The disease involves up to four joints and affects more than 50% of all children with JIA. Its onset usually occurs between the ages of one and three. The first worrying symptom may be difficulty in walking or frequent falls. Girls are affected 3–5 times more often than boys. Arthritis is asymmetrical, with the most commonly affected joints being the knee, wrist, ankle, elbow, and sometimes single interphalangeal joints of the hand. The hip or shoulder joint is rarely involved, and there are usually no spinal lesions. In most children, the disease does not involve more than four joints (persistent JIA), but about 30% of patients may develop symptoms in five or more joints after six months (extended JIA). Complications include flexion contractures, subluxations or joint instability. Lengthening or shortening of the limb can be a potential complication. The most serious symptom in this group of patients is uveitis. In addition, 30–65% of children have positive antinuclear antibodies (ANA), which is a risk factor for the development of uveitis, which is initially asymptomatic; therefore, according to the 2019 American College of Rheumatology (ACR) guidelines, it is mandatory for such patients to undergo a routine ophthalmological examination every three months. Untreated anterior uveitis can cause complications, such as glaucoma, cataracts or loss of visual acuity [1, 10–12].

Recommended therapies include non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular corticosteroids, conventional DMARDs such as methotrexate and sulfasalazine, and biological DMARDs such as TNF inhibitors [10, 13, 15].

RF-NEGATIVE POLYARTHRITIS

Polyarthritis manifests with inflammation of ≥ 5 joints as early as the first six months of the disease. RF-negative polyarthritis affects 15–20% of patients with JIA. It usually affects young girls between the ages of two and four. Its onset may be insidious, with the involvement of further joints in the subsequent course. Arthritis may be asymmetrical. In most patients, the temporomandibular joint is involved. In contrast, oligoarticular JIA is characterised by increased general inflammation, which may result in growth disturbances [1, 10–12].

Recommended therapies include NSAIDs, intra-articular and systemic corticosteroids, conventional DMARDs such as methotrexate, and biological DMARDs such as TNF and IL-6 inhibitors [10, 14, 15].

RF-POSITIVE POLYARTHRITIS

It is most common in adolescent girls (10:1 ratio of girls to boys) and affects approximately 5% of all patients with JIA. Joint involvement is symmetrical, most often affecting the small joints of the hands and feet, and resembles the spectrum of symptoms in adult RA. Tests often find elevated inflammatory markers. The course is characterised by rapid progression leading to joint destruction, as in RA. Complications include joint involvement of the cervical spine with possible subluxation of the C1 and C2 vertebrae. Extra-articular manifestations include rheumatoid nodules, associated with a more severe disease course, and vasculitis, as in RA [1, 10–12].

Recommended therapies include NSAIDs, intra-articular and systemic corticosteroids, conventional DMARDs such as methotrexate, and biological DMARDs such as TNF and IL-6 inhibitors [10, 14, 15].

SYSTEMIC JIA

It affects 5–15% of children with JIA and is the most severe subtype of the disease. It has no gender predilection and can occur throughout childhood, although the peak incidence is in the first five years of life. According to the ILAR definition, the disease can be diagnosed when a child presents with arthritis, recurrent fever above 39°C for two weeks, documented by a physician for three consecutive days, and one of the following symptoms: salmon-pink rash accompanying an increase in body temperature, lymphadenopathy, hepatosplenomegaly and/or serositis. Arthritis may not be present at the onset of the disease but may appear with a delay of up to six months and is typically polyarticular. Ap-

proximately 50% of children with systemic JIA achieve resolution of disease activity and remission. Its severe complication is macrophage activation syndrome (MAS), which is overtly clinical in approximately 10% of patients (30–40% of MAS have a subclinical course). It is a life-threatening condition associated with a high mortality rate and requires early diagnosis and aggressive treatment [1, 10–12].

Recommended therapies include systemic corticosteroids, conventional DMARDs such as methotrexate, and biological DMARDs such as IL-1 and IL-6 inhibitors [10, 13, 15].

JUVENILE PSORIATIC ARTHRITIS

It affects 3–10% of JIA patients. JPsA is diagnosed when a child has arthritis and psoriasis or arthritis without psoriasis, but at least two of the following criteria are met: dactylitis (swelling of the fingers/toes), nail pitting („thimble" sign) or onycholysis, or psoriasis in a first-degree relative. In most cases, JPsA can follow a similar course to oligoarticular JIA, but unlike the latter, it can also involve the shoulder joints, hip joints, spine, sacroiliac joints, and small joints of the hands or feet [10–12].

Recommended therapies include NSAIDs, intra-articular corticosteroids, conventional DMARDs such as methotrexate, and biological DMARDs such as TNF inhibitors and IL-17 blockers [10, 14, 15].

ENTHESITIS-RELATED ARTHRITIS

It affects 5–30% of JIA patients. According to ILAR criteria, it can be diagnosed when the patient has arthritis and enthesitis or only one of the above, but at least two of the following criteria are met: onset of arthritis in boys over six years of age, tenderness of the sacroiliac or lumbosacral joints, presence of HLA-B27 antigen, family history of HLA-B27-related diseases and/or acute anterior uveitis. ERA is the only subtype more common in boys (boys to girls 7:1). The HLA-B27 antigen is present in 50–90% of patients. Most commonly, the onset of the disease is between the ages of 10 and 13. Initially, it presents as oligoarthritis but affects the joints of the lower limbs, including the hip joints. Tarsal arthritis and enthesitis are typical, while axial skeletal involvement appears later in the course of the disease in patients with the HLA-B27 antigen. Acute uveitis is a possible extra-articular manifestation in 3–7% of children (pain, redness of the eye, photophobia) as opposed to asymptomatic uveitis in patients with oligoarticular JIA. Hip or sacroiliac joint involvement may occur, but axial skeletal involvement is less common than in adults with ankylosing spondylitis [1, 10–12].

Recommended therapies include NSAIDs, intra-articular and peritendon corticosteroids, conventional DMARDs such as sulfasalazine and methotrexate, and biological DMARDs such as TNF and IL-17 inhibitors [10, 14, 15].

UNDIFFERENTIATED ARTHRITIS

It affects 10–15% of patients with JIA and includes other types of arthritis not meeting the above criteria or meeting criteria for more than one diagnosis. Arthritis associated with inflammatory bowel disease (IBD) is most commonly included here. It manifests in 7–21% of patients with IBD. Polyarthritis is common, but sacroiliac joint or axial skeleton involvement is also frequent. Arthritis associated with IBD is considered a type of peripheral spondyloarthritis, and treatment of gastrointestinal complaints is crucial. When IBD is well controlled, joint symptoms subside, although in a small proportion of cases, methotrexate treatment is required [1, 3, 10–12].

MECHANISM OF ACTION OF JAK INHIBITORS

JAK inhibitors are small, orally applied molecules that inhibit the intracellular JAK-STAT signalling pathway. Tofacitinib (a JAK1/JAK3 inhibitor) and baricitinib (a JAK1/JAK2 inhibitor) belong to this group of medicines [6, 7].

JAKs/signal transducers and activators of transcription (STATs) are proteins that convert extracellular stimuli into intracellular activation or regulatory messages. JAKs are members of the tyrosine kinase family and are essential signalling mediators for cytokine receptors. The JAK family consists of four intracellular tyrosine kinases: JAK1, JAK2, JAK3 and TYK2. The binding of a cytokine to its receptor induces phosphorylation of the corresponding JAKs, which then switch to an activated state, leading to recruitment and activation by phosphorylation of the associated STATs. The STAT family includes seven molecules: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. Upon activation, the STAT complex translocates to the nucleus and induces transcription of the corresponding factor. This signalling

pathway is common to many pro-inflammatory cytokine receptors, such as IL-6, IL-2, IL-10 and interferon (IFN) type I and II receptors, and regulates the immune system and the inflammatory response [16].

Studies have shown that JAK/STAT signalling pathways are central to the pathogenesis of many autoimmune inflammatory conditions. JAK inhibitor therapies have been approved based on clinical trial results for the treatment of adult rheumatic diseases such as rheumatic arthritis (RA) and psoriatic arthritis (PSA). JAK inhibitors currently represent an important group of targeted synthetic LMPCHs that act as anti-inflammatory agents and prevent joint damage. Also, patients with monogenic type I interferonopathies, causing abnormal activation of the IFN I pathway, are treated with JAK inhibitors with promising outcomes [16, 17].

BARICITINIB CLINICAL TRIAL DATA

The JUVE-BASIS phase 3, randomised, double-blind, placebo-controlled trial assessed the efficacy and safety of baricitinib in treating JIA [7].

The trial involved 220 patients aged 2 to 18 years diagnosed with polyarticular JIA: RF-positive or negative, extended oligoarticular JIA, ERA, or JPsA, and inadequate response (after ≥ 12 weeks of treatment) or intolerance to one or more conventional synthetic or biological DMARDs. The trial included a two-week safety and pharmacokinetic period, a 12-week open-label lead-in period, and an up to 32-week placebo-controlled double-blind withdrawal period. Once dosing was established, patients received 4 mg or less of baricitinib (tablets or suspension) once a day.

At week 12, a response meeting the Juvenile Idiopathic Arthritis-American College of Rheumatology (JIA-ACR) 30 criteria was found in 74% of the patients. During the open-label lead-in, 26% of patients discontinued treatment: 17% due to lack of a JIA-ACR30 response, and the remainder for other reasons. At the end of the open-label lead-in, 76% of patients achieved a JIA-ACR30 response, 46% had a JIA-ACR70 response, and 7% had inactive disease as per JIA-ACR. The mean Juvenile Arthritis Disease Activity Score-27 (JADAS-27) decreased by 12.4 at the end of the open-label period compared with the baseline. All main response variables showed improvement from the baseline. In the phase 3 trial, the time to disease exacerbation was significantly shorter in the placebo group compared with the baricitinib group. Treatment-emergent adverse events were found in 126 (57%) of the 220 patients in the phase 1 and phase 2 trials. Six (3%) had serious adverse events in the phase 1 and phase 2 trials. In the phase 3 trial, serious adverse events were reported in 4 (5%) patients in the baricitinib group and 3 (4%) in the placebo group. In the phase 1 and 2 trials, 25% of patients reported treatment-emergent infections, and in phase 3, 38% in the baricitinib group and 19% in the placebo group. A pulmonary embolism was reported in one patient as a serious event, which was considered related to treatment with the medical product studied.

The trial demonstrated that baricitinib is effective and has an acceptable safety profile for the treatment of JIA after inadequate response or intolerance to standard therapy [7]. This trial was the basis for a new indication for using baricitinib in JIA therapy [8].

Other JAK inhibitors are currently being investigated as therapy for JIA, so information on new indications, including uveitis in JIA, and the use of new drugs from this group in the treatment of JIA should be expected [18].

TOFACITINIB CLINICAL TRIAL DATA

The first phase 1 tofacitinib trial for treating JIA developed a weight-dependent dosing regimen for tablets and oral solutions for patients aged ≥ 2–18. The taste of the drug was also confirmed to be well tolerated by children [6].

The objective of the subsequent 44-week randomised, double-blind, placebo-controlled phase 3 trial was to assess the efficacy and safety of tofacitinib compared with placebo in JIA patients [19]. It involved 225 patients diagnosed with extended oligoarthritis, RF-positive polyarthritis, RF-negative polyarthritis, systemic JIA without active systemic features, JPsA, or ERA. Inclusion criteria specified disease activity, with polyarticular JIA requiring an insufficient response to one or more DMARDs (methotrexate or a biological drug). Patients diagnosed with JpSA or ERA were included in the study if they inadequately responded to NSAID therapy. During the first part of the study, patients received the drug in an open-label trial for 18 weeks. Participants with at least 30% improvement by JIA-ACR30 criteria were randomly assigned (1:1) to continue treat-

ment with tofacitinib or a receive placebo in the second part of the study for 26 weeks. Depending on body weight, the patients received 5 mg or less of tofacitinib twice a day. In addition, 65% of participants received concomitant methotrexate. A 54% reduction in the risk of exacerbation was shown in tofacitinib-treated patients compared to those receiving placebo. The study also demonstrated rapid improvement after treatment initiation, with JIA-ACR30 criteria improvement of ≥ 30% achieved as early as week 2 of therapy. In addition, 26% of patients treated for 44 weeks achieved an inactive disease. In the second part of the study, adverse events occurred in 77% of patients receiving tofacitinib and 74% of patients in the placebo group. Serious adverse events were reported in one (1%) and two (2%) patients, respectively. Over the entire tofacitinib treatment, 48% of patients experienced infections or infestations. No deaths were reported during the study. The results of this pivotal study demonstrated that tofacitinib is an effective therapy for the investigated JIA subtypes [19]. It was the basis for the registration of the drug for JIA treatment [9].

The most recent 2024 study presents long-term follow-up results, including safety, tolerability and efficacy of tofacitinib in patients diagnosed with JIA [20]. Patients aged 2–18 years who received the drug in previous trials treatment with tofacitinib was continued at doses of 5 mg twice daily or less, depending on body weight. The median and range of treatment duration were 41.6 and 1–103 months, respectively.

Among patients with polyarticular JIA, JIA-ACR70/90 responses were achieved in 60% and 34% of participants, respectively, at month 1 of treatment and generally improved over time. By month 48 of follow-up, JIA exacerbations affected less than 5% of patients. The average disease activity per JADAS-27 was 22.0 at the baseline, 6.2 at month 1 and 2.8 at month 48. Inactive disease was found at month 1 of treatment in 28.8% and month 48 in 46.8% of patients. Clinical efficacy was maintained for at least 48 months of therapy.

During this time, adverse events were reported in 89.3% of treated patients, of which serious adverse events were reported in 15.1%. The most common adverse events were upper respiratory tract infections (21.3%), JIA exacerbation (12.4%) and nasopharyngitis (12%). Ten patients developed serious infections: three cases of herpes zoster and single cases of limb abscess, COVID-19, pyelonephritis, infectious mononucleosis, molluscum contagiosum, rhinovirus infection, and urinary tract infection. All cases of herpes zoster resolved after treatment. Two patients developed mild uveitis that did not require a change in systemic treatment.

Adverse events led to permanent discontinuation of study participation in 13.9% of patients. A positive interferon-gamma release assay, found in three patients, was the most common reason for discontinuation. Other reasons included arthritis/acute disease, pregnancy or spontaneous abortion, herpes zoster, and a suicide attempt. In addition, 36.9% of patients were temporarily discontinued or had their dose reduced due to adverse events, mainly infections, less commonly abnormal laboratory results, which included leucopenia and neutropenia, increased creatine kinase or aspartate transferase (AST)/alanine transaminase (ALT) activity in the blood.

The study confirmed a safety profile for the drug consistent with the results of the phase 3 trial. No deaths or cases of tuberculosis, MAS, interstitial lung disease, malignancies, thrombotic or other events were reported.

These interim results confirm the safety of tofacitinib as an effective oral option for long-term use in patients with JIA. The publication of the final results of the study is planned, which will provide even more information on the long-term benefit-to-risk profile of tofacitinib in patients diagnosed with JIA [19].

REGISTER OF MEDICINAL PRODUCTS

Currently, the Register of Medicinal Products Authorised for Marketing in the Republic of Poland [21] lists two JAK inhibitors with JIA indications: baricitinib (trade name Olumiant, tablets 1 mg, 2 mg, 4 mg) and tofacitinib (trade name Xeljanz, oral solution 1 mg/ml; tablets 5 mg).

According to the summary of product characteristics (SPC), Olumiant (baricitinib) is indicated for the treatment of active JIA in patients aged 2 years and older who have had an inadequate response to or are intolerant of treatment with at least one synthetic or biological DMARD for JIA polyarticular RF+ or RF–, extended oligoarthritis, ERA, JPsA.

Baricitinib can be used as monotherapy or in combination with methotrexate [8, 21].

Xeljanz (tofacitinib) is indicated for the treatment of active polyarticular JIA (RF-positive or -negative polyarthritis and extended oligoarthritis) and JPsA in patients aged 2 years and older who have had an inadequate response to prior treatment with DMARDs. Tofacitinib can be used in combination with methotrexate or as monotherapy when methotrexate is intolerant or when further treatment with methotrexate is inappropriate [9, 21].

JAK INHIBITORS IN JIA TREATMENT

According to the clinical trial results presented above and the registered indications, baricitinib and tofacitinib are indicated for patients aged 2 years and older diagnosed with selected JIA subtypes as the second-line treatment after failed therapy with conventional synthetic or biological DMARDs.

Table 1 lists the JIA subtypes and medicine doses.

GENERAL INFORMATION ON JIA MANAGEMENT WITH JAK INHIBITORS

Exact information is contained in the SPC, the knowledge of which is the responsibility of the treating doctor.

Treatment should be undertaken and supervised by a specialist experienced in diagnosing and treating JIA. The benefits and risks of the treatment should be carefully weighed each time.

ADVICE BEFORE STARTING TREATMENT

JAK inhibitors can be used in combination with conventional DMARDs such as methotrexate. However, combining JAK inhibitors with biologics or potent immunosuppressive drugs such as cyclosporine should be undertaken very carefully, given the potential for more severe immunosuppression and the lack of safety data [22].

Before starting medication, it is recommended that the patient have a history of allergies and infectious diseases, including smallpox, herpes zoster, opportunistic infections, and severe infections such as toxoplasmosis, tuberculosis, and pneumococcal infection.

A thorough physical examination should also be performed.

Laboratory investigations should include at least a blood count, liver and kidney tests, urinalysis, and serology for viral infections: human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), varicella zoster virus (VZV) and interferon-gamma release assays (IGRA) or tuberculin skin test (TST) A chest X-ray and electrocardiogram (ECG) should be performed in patients.

Table 1. Indications for treatment with Janus kinase (JAK) inhibitors and doses in patients with juvenile idiopathic arthritis (JIA) according to the summary of product characteristics (SPC) [21]

Medicine Patient's age	JIA subtype	Route of administration/dosage form Dose
BARICITINIB Children ≥ 2 years	RF-positive polyarthritis; RF-negative polyarthritis; Extended oligoarthritis ERA JPsA	Oral Tablets 1 mg, 2 mg, 4 mg Body weight: ≥ 30 kg: 4 mg 1 ×/day 10 – < 30 kg: 2 mg 1 ×/day Dissolving the tablet in water may be considered
TOFACITINIB Children ≥ 2 years	RF-positive polyarthritis; RF-negative polyarthritis; Extended oligoarthritis JPsA	Oral Solution 1 mg/ml; tablet 5 mg Body weight: 10 - < 20 kg: 3.2 mg 2 ×/ day 20 - < 40 kg: 4 mg 2 ×/day ≥ 40 kg: 5 mg 2 ×/day Due to the need to adjust the dose according to body weight, patients < 40 kg require an oral solution

RF — rheumatoid factor; ERA — enthesitis-related arthritis; JPsA — juvenile psoriatic arthritis

An assessment of the coagulation system with antiphospholipid antibodies and a full lipid profile test should be considered.

Investigations should include an assessment of potential and current extra-articular manifestations of the disease and adverse events.

Based on existing evidence and due to the increased risk of infection with JAK inhibitor use, it is suggested to ensure that vaccines are administered to children likely to start treatment. In patients who have not had chickenpox, vaccination against VZV should be considered; JAK inhibitor treatment can be started one month later [16].

Flu and pneumococcal vaccines should be administered according to schedule.

It is recommended that JAK inhibitors be withheld for one to two weeks (if disease activity permits) after each dose of the COVID-19 vaccine [22].

MONITORING DURING TREATMENT

Disease activity monitoring should be standard for JIA: monthly during the first three months of treatment, then every three months with the assessment of disease activity markers, depending on the subtype.

Safety monitoring of treatment should include the following:

— at each visit:
  - a thorough history, including infection history,
  - a full physical examination,
  - additional examinations: blood count, liver and kidney tests, urinalysis,
  - evaluation of extra-articular manifestations;
  - after 1–2 months of therapy it is advisable to perform a lipidogram,

— periodically, at least once a year:
  - IGRA and chest X-ray [15].

Monitoring viral replication by polymerase chain reaction (PCR) is recommended to evaluate viral infections [15].

Monitoring of growth, sexual maturation and bone metabolism is indicated [16].

DRUG PROGRAMME

In drug programme B33: *Treatment of patients with active RA and JIA [in the International Statistical Classification of Diseases and Related Health Problems (ICD-10:) M05, M06, M08], the JAK inhibitors baricitinib, tofacitinib, upadacitinib, filgotinib are listed in the RA section.* the drug tofacitinib was added on October 1, 2024 [23].

According to the programme B33 [23]:

Patients aged 2 years and older who meet the following diagnostic criteria may be eligible for tofacitinib therapy:

— polyarticular JIA with at least five swollen joints and at least three joints with limited mobility and soreness, accelerated erythrocyte sedimentation rate (ESR) or elevated C-reactive protein (CRP) and disease activity assessed by a doctor of at least 4 points on a 10-point scale, despite treatment with two DMARDs/immunosuppressants listed in the programme at the current doses (including methotrexate) for a minimum of three months each

or

— oligoarticular JIA, extended and persisting for more than six months, with factors of poor prognosis (according to ACR) and at least two swollen joints or joints with limited mobility and pain and disease activity assessed by a doctor as having at least 5 points on a 10-point scale with accompanying pain, tenderness or both, despite treatment with two of the DMARDs/immunosuppressants listed in the programme at the current doses (including methotrexate) for a minimum of three months each

or

— JPsA according to ILAR criteria with at least three swollen joints or with limited mobility and tenderness and at least one active (or history of) enthesitis or with active sacroiliac arthritis in patients with intolerance or unsatisfactory response to at least one NSAID used at the maximum recommended or patient-tolerated dose for one month, unless contraindicated, and intolerance or unsatisfactory response to at least one DMARDs used at the patient's maximum recommended or tolerated dose for two months, unless contraindicated.

DOSES

Tofacitinib should be dosed as specified in the current SPC, taking into account the recommendations of the European Alliance of Associations for Rheumatology/ American College of Rheumatology (EULAR)/ACR, including the option to reduce the dose or extend the interval between doses

in patients in whom the treatment goal has been achieved.

COMMENTARY ON THE PROGRAMME

According to treat to target (T2T) recommendations for JIA, the therapy used is expected to result in a rapid reduction in disease activity. For oligoarticular and polyarticular JIA, the programme provides for the inclusion of DMARDs after the proven failure of two conventional DMARDs (three months of therapy each). This implies the persistence of disease activity for six months until the inclusion of another drug, such as a JAK inhibitor. If conventional DMARDs are ineffective, efforts should be made to change the medicine earlier and achieve inactive disease state.

According to the drug programme [23], a drug may be included for JPsA patients after NSAID ineffectiveness; however, the SPC recommends it after at least one conventional or biological DMARD has been deemed ineffective. JAK inhibitors are recommended as the second-line treatment.

CONCLUSIONS

Children with JIA have an opportunity to access modern JAK inhibitor therapy.

To date, the efficacy and good safety profile of two drugs from this group have been proven: baricitinib and tofacitinib.

JAK inhibitors are recommended for the following subtypes of JIA: extended oligoarthritis, RF-positive polyarthritis, RF-negative polyarthritis, and JPsA in patients aged ≥ 2 years. Baricitinib is additionally recommended for ERA patients of the same age.

The use of JAK inhibitors does not replace conventional therapeutic strategies in JIA patients. These drugs are recommended as second-line treatment after at least one conventional or biological DMARD has been found to be ineffective. JAK inhibitors may be an effective alternative therapy in severe, complicated and refractory JIA.

The benefit-to-risk ratio should be determined each time therapy is initiated.

The long-term effects of treatment with JAK inhibitors are currently unknown, especially in children.

JAK inhibitors are oral drugs with an acceptable taste, so they can be a viable alternative in children intolerant of injections.

Their inclusion in the drug programmes of the Ministry of Health is a prerequisite for their widespread availability for children with JIA.

AUTHORS' CONTRIBUTION

All co-authors contributed equally to the article. V.O.W.: concept, assumptions, data analysis, writing of the article, final proofreading. E.S.: concept, assumptions, data analysis, writing the article, final proofreading.

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CONFLICT OF INTEREST

Potential conflict of interest: V.O.W. — one-time participation in a Pfizer advisory meeting; E.S. — one-time participation in a Pfizer advisory meeting.

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