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Secukinumab in the treatment of patients with juvenile idiopathic arthritis categories of enthesitis-related arthritis and juvenile psoriatic arthritis — an experts' opinion of the Polish Society of Rheumatology and the Section of Developmental Age Rheumatology of the Polish Society for Rheumatology

ABSTRACT

According to the juvenile idiopathic arthritis (JIA) classification criteria there are two categories of the disease within the spondyloarthropathies spectrum — enthesitis-related arthritis (ERA) and juvenile psoriatic arthritis (JPsA). These are chronic rheumatic paediatric diseases, that manifest themselves with heterogeneous clinical symptoms and comorbidities, resulting in pain, growth and development impairment, deteriorated physical fitness and lowered health-related quality of life. Juvenile spondyloarthropathies may occur in 25 percent of patients with JIA. The age of onset usually is above 10, but it happens that correct diagnosis is delayed by a few years. Problems with a diagnosis of axial spondyloarthropathy in children may arise from the fact, that inflammation of the sacroiliac joints may be clinically silent at the beginning of the disease, which results in lesser sensitivity of the Assessment in SpondyloArthritis international Society classification criteria for axial spondyloarthropathies in paediatric practice. Concurrently it is key to rapidly introduce effective treatment, that should enable proper development and further life without active inflammation and its long-term complications. Guidelines for the pharmacotherapy of children with JIA include the use of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids (GCSs), classic disease-modifying anti-rheumatic drugs (cDMARDs) and biological treatment. Amongst biologics, drugs that for a long time are used in various categories of JIA are medications out of the TNF-α inhibitors group. Unfortunately, there is a large group of patients for whom such therapy is inadequate or unavailable (no biological therapy is currently reimbursed in the ERA and JPsA categories). This leads to prolonged corticosteroid therapy, the complications of which are drastic for a growing child. Out of therapies with a different mechanism of action, in the population of patients with ERA and JPsA inhibiting interleukin 17 (IL-17) proved to be effective.

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One medication out of this group — secukinumab (SEC) — in June 2022 was granted market authorization for use in these disease categories based on the findings of the JUNIPERA clinical registration trial. This study demonstrated that SEC (added to the option to use conventional disease-modifying anti-rheumatic drugs — SEC ± cDMARDs) allows a statistically significant reduction of the disease flare risk by 72% in comparison to the PLC ± cDMARDs group. What is more, better results have been attained in the SEC group with regard to such clinical symptoms as: JIA ACR 30, 50, 70, 90, and 100 responses, inactive disease status, enthesitis count, or the active joint count. During the JUNIPERA trial no deaths have been recorded. Differences in the adverse events rates between the SEC and placebo groups were small and clinically insignificant. The rate of serious adverse events was low both in the SEC treatment group as well as placebo. The above results show that patients with ERA and JPsA have gained a new effective and safe therapeutic option, that addresses an unmet medical need in that group of patients. Adequately rapid implementation of IL-17 inhibitors may prevent mobile disability and extra-articular damage in patients with ERA and JPsA.

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KEY WORDS: secukinumab; interleukin 17A; juvenile idiopathic arthritis; enthesitis-related arthritis; juvenile psoriatic arthritis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic, immune-mediated systemic connective tissue disease of the developmental age. According to the International League of Associations for Rheumatology (ILAR) criteria, JIA refers to arthritis beginning before the age of 16 years and lasting at least six weeks, after all known causes of arthritis have been excluded [1, 2].

The course of JIA is chronic, with periods of exacerbation and remission. The clinical picture of the disease is heterogeneous. Irrespective of the clinical category of the disease, the hallmark feature of JIA is joint inflammatory involvement, which is clinically manifested by swelling and impaired function. Due to the ongoing inflammatory process, joint structures are damaged and, in the case of an aggressive course of the disease, the child's growth may be stunted or internal organs may be involved [3–5].

Advances in research into the pathogenesis of the disease offer the opportunity for increasingly effective treatments. Over the years, the attention of researchers has focused on the role of tumour necrosis factor alpha (TNF-α) and drugs that inhibit its activity. The last decade has provided evidence of the important role of the interleukin-17/interleukin-23 (IL-17/IL-23) pathway in the development of spondylarthritis (SpA), providing the rationale for clinical trials to assess the efficacy of IL-17A inhibition in patients with this disease [6].

Secukinumab (SEC) is one of the IL-17 inhibitors, which demonstrated clinical efficacy over placebo in the JUNIPERA registration trial (NCT03031782): SEC ± conventional disease-modifying antirheumatic drugs (cDMARDs) *vs.* PLC ± DMARDs in two clinical disease categories: enthesitis-related JIA and juvenile psoriatic arthritis (JPsA) [7].

Based on this study, SEC was registered by the European Medicines Agency (EMA) for use in these JIA categories for people over 6 years of age [8].

Currently, no biologic drug is registered and reimbursed in such a defined patient population [9].

CLINICAL PRESENTATION AND EPIDEMIOLOGY OF JUVENILE SPONDYLOARTHROPATHIES

Due to the heterogeneity of the clinical picture observed during the first 6 months of the disease and the differences in the results of laboratory diagnostic tests, ILAR distinguishes 7 clinical categories of JIA [1]:

— systemic JIA;
— oligoarticular/pauciarticular JIA;
— RF-positive polyarticular JIA;
— RF-negative polyarticular JIA;
— enthesitis-related JIA;
— juvenile psoriatic arthritis (JPsA);
— undifferentiated JIA.

As part of complex of diseases such as JIA, juvenile spondyloarthropathies are conventionally represented by enthesitis-related JIA and JPsA; however, in many cases, due to the evolution of symptoms in the course and the expansion of diagnostic possibilities, other seronegative clinical categories of JIA should be included, mainly oligoarticular/pauciarticular JIA and polyarticular JIA, as well as undifferentiated JIA.

The diagnosis of enthesitis-related JIA can be established in a child in the case of co-occurrence of arthritis and enthesitis, or in the case of isolated arthritis or enthesitis when at least two of the following criteria are met at the same time [3, 5]:

— sacroiliac joint pain or inflammatory low back pain (current or past history);
— positive HLA B27 antigen;
— onset of symptoms in a boy over 6 years of age;
— past or present acute anterior uveitis;
— family history (in first-degree relatives) of ankylosing spondylitis, enthesitis-related arthritis, sacroiliac arthritis with inflammatory bowel disease (IBD) or acute choroiditis.

It is the only clinical presentation of JIA that is more common in boys.

The diagnosis of JPsA can be established when there is a co-occurrence of at least 6 weeks of arthritis with psoriatic skin lesions or at least two of the following symptoms [3, 5]:

— *dactylitis* — classified as swelling in one or more joints of the fingers that extends beyond the joint margin;
— punctuate lesions of nails or onycholysis — (thimble-like appearance of a minimum of 2 or more punctate lesions within the nail plate);
— psoriasis in a first-degree relative.

In the majority of JPsA patients, arthritis may precede the appearance of typical psoriatic skin lesions by many years, and thus other categories of JIA are diagnosed based on the number of joints involved — oligoarticular/pauciarticular JIA and polyarticular JIA or undifferentiated JIA. Clinical signs such as nail lesions, *dactylitis* and a positive family history may determine the change of initial diagnosis to JPsA in subsequent years of the disease course.

The average age of onset for enthesitis-related JIA is approximately 10–12 years, and the diagnostic delay can be compared to that in adult patients and is approximately 6 years. The diagnostic difficulties in rapidly establishing the diagnosis are most likely due to the different onset of the disease in children compared to adult patients. In children, enthesitis or inflammation of peripheral joints of the lower limbs is the first symptom of the disease in approximately 95% of those suffering from this form of disease, while typical inflammatory back pain is present in only under 5% [6]. Recent data show that the prevalence of different forms of JIA changes significantly with age. In children under the age of 5 years, oligoarticular/pauciarticular JIA is by far the predominant form of disease, while enthesitis-related JIA is not present at all (by definition), and JPsA and undifferentiated JIA represent 12%. At the age of 5–11 years, forms that may include juvenile spondyloarthritides are already diagnosed in 18% of children, while in those older than 11 years — up to 38% (enthesitis-related JIA + JPsA + undifferentiated forms) [10].

In Poland, based on data from the Małopolska Province, it can be inferred that children with enthesitis-related JIA and JPsA represent at least 12–24% of the total population with JIA [11]. In general, epidemiological data on the incidence of JIA vary considerably between countries and range from 1.6 to 23 per 100 000 (based on a European publication) [12]. According to other sources, the incidence of the arthropathy in question ranges from approximately 4 to 14 cases per 100 000 children of the global population (no data specific to Poland are available). In Poland, 5.6–9.5 new cases are diagnosed annually per 100 000 population under 18 years of age [11]. The differences found in the epidemiological data are probably due to the heterogeneous definitions and criteria for the diagnosis of arthropathies used in different regions of the world and the exposure of genetically predisposed children to different environmental factors.

CONVENTIONAL TREATMENT OF ENTHESITIS-RELATED JIA AND JPsA

Treatment of JIA aims to eliminate or minimise inflammatory activity, thereby preventing the development of complications, including progressive musculoskeletal, visual, internal organ dysfunctions, developmental disorders, osteoporosis, and amyloidosis-related complications of the disease, and preventing stunted growth. The treatment should be initiated as soon as the diagnosis is established. Guidelines for the pharmacotherapy of children with JIA include the use of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids (GCSs) administered intra-articularly, briefly (up to 3 months) and systemically, cDMARDs and biologic DMARDs (bDMARDs).

NSAIDs are among the commonly used pharmaceuticals in the treatment of JIA with analgesic, antipyretic and anti-inflammatory effects. For patients with involvement of the peripheral joints, entheses or

fingers, methotrexate (MTX) or sulphasalazine (SSA) are recommended in addition to the use of NSAIDs in mild cases and, in justified cases, treatment with GCS [6]. Other therapeutics in this group include hydroxychloroquine or cyclosporine A. Failure of cDMARD therapy is an indication for the use of bDMARDs, primarily from the TNF inhibitor group or a biologic drug that inhibits IL-17A activity [13].

BIOLOGICAL TREATMENT AND JPsA

Biological drugs mentioned in recommendations for the therapeutic management of various forms of JIA include TNF inhibitors (adalimumab, etanercept), IL-1 receptor antagonists (anakinra, canakinumab, rilonacept), IL-6 (tocilizumab), and drugs that modulate T-lymphocyte costimulation (abatacept). Adalimumab, etanercept, tocilizumab and anakinra are reimbursed in Poland for the treatment of JIA under the current B.33 drug programme "Treatment of patients with an active form of rheumatoid arthritis and juvenile idiopathic arthritis (ICD-10: M05, M06, M08)" but in clinical categories other than enthesitis-related JIA and JPsA. Despite the American College of Rheumatology (ACR) 2019 recommendation, enthesitis-related JIA and JPsA are not included in the B.33 drug programme and thus biological therapy is not available for this patient group.

In June 2022, based on the JUNIPERA registration trial, the first and so far only IL-17A inhibitor, SEC, was registered by EMA as monotherapy or combined therapy with MTX for the treatment of active enthesitis-related JIA or active JPsA, in patients older than six years of age who have not achieved an adequate response to conventional drugs or who cannot tolerate conventional treatment [8].

The availability of SEC in the drug programme would make it possible to treat this group of patients also in Poland. In terms of other recommended bDMARDs and synthetic DMARDs, adalimumab is registered for the treatment of enthesitis-related JIA for people older than 6 years of age, etanercept for the treatment of enthesitis-related JIA and JPsA for those aged 12 years and older, and tofacitinib for the treatment of JPsA for those older than 2 years of age. None of the aforementioned therapies are also available in Poland for the treatment of enthesitis-related JIA and JPsA.

ROLE OF IL-17 IN THE PATHOGENESIS OF INFLAMMATORY SPONDYLOARTHROPATHIES

In the early days of research into the pathogenesis of spondylarthritis, a key role in the inflammatory process was attributed to Th1 lymphocytes and the TNF-α cytokine. Subsequent years brought evidence of the important role of the IL-17/IL-23 pathway in the development of the disease, which formed the basis for the initiation of clinical trials evaluating the efficacy of IL-17A inhibition in SpA patients. Interleukin-17A is produced by many cells that play an important role in the induction and maintenance of inflammation, such as macrophages, mast cells, neutrophils and Th17 lymphocytes belonging to the T helper cell population but also cytotoxic lymphocytes and gamma/delta T cells. Interleukin-17A affects numerous cells involved in the pathogenesis of inflammation in SpA, such as macrophages, neutrophils, keratinocytes, endothelial cells, fibroblasts, chondrocytes, osteoblasts, and osteoclasts [14].

The pathogenesis of enthesitis-related JIA is not well understood, the prevailing view is that it is determined by HLA-B27-mediated presentation of iatrogenic peptides in association with T-cell activation and secretion of IL-23 and IL-17. Inflammation of the intestinal wall, often concomitant with enthesitis-related JIA, is associated with activation of T $\gamma\delta$ lymphocytes, innate type 3 lymphoid cells, Th17 lymphocytes, and production of IL-17 and IL-23. Enthesitis is triggered by repetitive biomechanical stress stimulation, resulting in microtrauma and the release of fibronectin, hyaluronan and other molecular components from damaged connective tissue, which can directly activate synovial macrophages, stroma cells and IL-23 production, resulting in a positive feedback loop.

Juvenile psoriatic arthritis is marked by autoreactive T cells and the presence of autoantibodies, and usually shows a strong association with MHC class II alleles. The distribution of immune self-tolerance includes MHC class II alleles, suggesting a key role for T helper cells. Inflammation is thought to be a consequence of an imbalance between the activity of pro-inflammatory Th1/Th17 lymphocytes and anti-inflammatory regulatory T cells (Treg). A decrease in the number of Treg cells was found to correlate with an increase in the Th17 lymphocyte population and is due to IL-1β-mediated differentiation

of naive T cells into Th cells. An increase in the release of the pro-inflammatory IL-17 induces the production of IL-6, MMP1 and 3, IL-8 (a neutrophil chemoattractant) by synoviocytes, resulting in the damage to joint structures. Importantly, the pathogenesis of JPsA shows similarities with enthesitis-related JIA and inflammation of the intestinal wall. Juvenile psoriatic arthritis with onset occurring in preschool and early school age is marked by the involvement of adaptive immune mechanisms in the development of dactylitis [15].

THE EFFICACY OF SEC IN PATIENTS WITH ENTHESITIS-RELATED JIA AND JPsA

Secukinumab is a fully human IgG1k monoclonal antibody directed against IL-17A. The SEC action targets IL-17A and inhibits the interaction of IL-17A with the receptor for IL-17. Consequently, SEC inhibits the release of pro-inflammatory cytokines, chemokines and mediators of tissue damage and reduces the involvement of IL-17A in the pathogenesis of autoimmune and autoinflammatory diseases.

The efficacy and safety of SEC in patients with enthesitis-related JIA and JPsA was assessed in 86 patients in the three-part, randomised, event-driven, double-blind, placebo-controlled phase III JUNIPERA trial. The trial included patients aged between 2 and 18 years with active enthesitis-related JIA and JPsA diagnosed based on the modified ILAR classification criteria. The trail consisted of an open part 1 in which all participants received SEC until week 12. Patients who had at least a 30% response to treatment according to the JIA-ACR criteria at week 12 were randomised in a 1:1 ratio to a double-blind phase II trial in which they continued SEC treatment or started placebo treatment until week 104 or until disease exacerbation occurred. The primary endpoint was time to disease exacerbation and the major secondary endpoints included response to treatment according to JIA ACR 30, 50, 70, 90 and 100 criteria; inactive disease, JADAS-27 activity score, number of entheses involved in inflammation, number of fingers involved in inflammation, number of active joints and safety of therapy. Disease exacerbation was defined as a worsening of at least 30% in at least 3 out of 6 JIA-ACR response criteria and an improvement of at least 30% in no more than 1 out of 6 JIA-ACR response criteria and a minimum of 2 active joints.

The clinical categories of JIA patients at the time of entry into the study included 60.5% of patients with enthesitis-related JIA and 39.5% of patients with JPsA who had an inadequate response or intolerance to treatment with at least 1 cDMARD and at least 1 NSAID. At baseline, MTX use was reported in 65.1% of patients (63.5% [33/52] of patients with enthesitis-related JIA and 67.6% [23/34] of patients with JPsA). Twelve out of 52 patients with enthesitis-related JIA were concurrently treated with SSA (23.1%). Patients weighing less than 50 kg at baseline (n = 30) received a dose of 75 mg, and patients weighing at least 50 kg (n = 56) received a dose of 150 mg. At baseline, the age of patients ranged from 2 to 17 years, with three patients aged between 2 and under 6 years, 22 patients were aged between 6 and under 12 years and 61 patients were aged between 12 and under 18 years. The initial disease activity score (DAS) according to the JADAS-27 index was 15.1 (standard deviation [SD] 7.1) and the mean number of entheses involved in inflammation was 2.6.

At the end of part 1 of the study, 75 out of 86 patients (87.2%) exhibited a JIA ACR 30 response and began participation in part 2 of the study. At week 12, also 83.7%, 67.4% and 38.4% of patients achieved JIA ACR 50, 70 and 90 responses, respectively. The beginning of the SEC action already occurred at week 1. At week 12, The JADAS-27 index was 4.64 (SD 4.73) and the mean reduction in the JADAS-27 index from baseline values was –10.487 (SD 7.23) [16].

In part 2 of the study, disease exacerbation occurred in 10 patients in the SEC-treated group and 21 patients treated with placebo — the risk of exacerbation was reduced by 72% in SEC-treated patients compared with placebo-treated patients (risk ratio = 0.28; 95% CI [confidence interval]: 0.13 to 0.63; $p < 0.001$). The percentage of responses according to the JIA-ACR 30, 50, 70, 90 and 100 criteria and inactive disease status were found in 89.2%, 78.4%, 67.6%, 51.4%, 43.2% and 47.2% of patients in the SEC group (n = 37) and 64.9%, 62.2%, 43.2%, 40.5%, 37.8% and 37.8% of patients in the placebo group (n = 37), respectively [17].

Using the NRI method, in which missing values are treated as non-response, those percentages were 54.1%, 51.4%, 51.4%, 43.2%, 37.8% and 40.5% in the SEC group (n = 37) and 39.5%, 39.5%, 39.5%, 39.5%, 39.5%, 36.8% and 36.8% in the placebo group (n = 38), respectively.

The mean change in JADAS-27 score was greater at the end of period 2 in the SEC group than in the placebo group: –13.3 *vs.* –12.9; similarly, mean change in number of entheses involved in inflammation: –2.1 *vs.* –1.9 and number of affected joints with active disease: –6.8 *vs.* –5.5 [18].

SAFETY PROFILE OF SEC IN CLINICAL TRIALS

The incidence of adverse events and serious adverse events throughout the treatment period in the SEC ± DMARD group was 91.7% and 14.6%, respectively, and was similar to the placebo group, in which, during the double-blind phase, the incidence of adverse events and serious adverse events throughout the treatment period was 92.1% and 10.5%, respectively [18].

There were no new safety signals in patients receiving SEC (injection site reaction, n = 1; total patient-years = 141.5) [17, 18].

The safety profile of SEC is consistent with the overall safety profile based on existing extensive data in many other indications: psoriasis, psoriatic arthritis, axial spondyloarthropathies [17].

SEC IN THE TREATMENT OF PATIENTS WITH ENTHESITIS-RELATED JIA AND JPsA

The results of the JUNIPERA trial confirm that SEC has a practical application in the treatment of patients with enthesitis-related JIA and JPsA. The drug can be used as a first-line treatment both after failure of NSAID therapy and after failure of TNF inhibitor therapy.

The recommended dose is calculated based on body weight (at body weight < 50 kg — 75 mg, and at body weight ≥ 50 kg — 150 mg) and administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, and monthly thereafter.

The positioning of biologics in patients with enthesitis-related JIA and JPsA in daily clinical practice requires knowledge of the mechanism of action, safety profile and clinical efficacy for both articular — axial and peripheral — manifestations, including, for example, enthesitis and dactylitis, and non-articular manifestations, such as uveitis, psoriasis and IBD.

CONCLUSIONS

Secukinumab is an IL-17A inhibitor biologic drug with efficacy and safety proven in the JUNIPERA trial in patients with enthesitis-related JIA and JPsA. The use of specific therapies, including SEC, in the treatment of patients with enthesitis-related JIA and JPsA should follow current recommendations and be in line with current medical knowledge. The decision should be made by a specialist in rheumatology, taking into account the clinical manifestations of the disease, disease activity, risk factors for severe disease, individual preferences of the patient or their caregiver, and the safety profile of the therapy. In Poland, access to SEC for patients with enthesitis-related JIA and JPsA depends on reimbursement of the drug under the drug programme. In the light of the above data, the experts of the Section of Developmental Age Rheumatology of the Polish Society of Rheumatology see an urgent need to increase the arsenal of modern drugs in the treatment of the two categories of JIA in question, including SEC with appropriate drug registration.

CONFLICT OF INTEREST

None declared.

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