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Recognition and treatment of autoinflammatory diseases in Poland – where are we in 2021?

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Authors:

Beata Wolska-Kuśnierz[1]
orcid.org/0000-0003-4863-4443
Ewa Więsik-Szewczyk[2]
orcid.org/0000-0001-8509-4453

1 - Immunology Department,
Children's Memorial Health Institute, Warsaw, Poland

2 - Department of Internal Medicine, Pulmonology, Allergy and Clinical Immunology, Central Clinical Hospital of the Ministry of NationalDefense,
Military Institute of Medicine, Warsaw, Poland

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Corresponding author: Beata Wolska-Kuśnierz b.wolska-kusnierz@ipczd.pl

Abstract

Systemic autoinflammatory diseases (SAIDs) were first defined as a separate and new group of diseases only 20 years ago. Inflammasomes which are a type of intracellular multiprotein platform that triggers the production of IL-1β plays a predominant pathogenic role. This translates into clinical practice since biologics that block IL-1 activity are effective treatment option. By 2017, Polish patients did not have access to reimbursed treatment with IL-1 blockers. The breakthrough came in October 2017 with the launch of the Congenital Autoinflammatory Syndromes Treatment Programme, reimbursed by the Ministry of Health and coordinated by the Autoinflammatory Diseases Section of the Rare Diseases Team. Since then anakinra, short acting Il-1 blocker is available for polish patients. Currently (Feb 2021), 25 pediatric patients and 31 adults were reported to receive anakinra. Based on the results of CLUSTER study canakinumab, long lasting Il-1 blocker is recommended in CAPS, TRAPS and MKD. As in other European countries, physicians and patients should have the option to choose an optimal, individually tailored therapy. Both, short and long lasting, interleukin-1 blockers should be available and reimbursed for both pediatric and adult patients. Taking into consideration the aspects of treatment: efficacy and safety as well as the patient's quality of life and preferences is of central important because most patients require continued, systematic and most likely lifelong treatment. We present the experience to date in the qualification of patients for treatment with interleukin 1 blockers, evaluation of treatment results during the drug program. We present challenges that may improve the diagnosis and therapy of patients with autoinflammatory diseases in Poland

Introduction

Systemic autoinflammatory diseases (SAIDs) were first defined as a separate and new group of diseases only 20 years ago. In 1999, TNFSFR1 mutations responsible for TRAPS were discovered.[1] Since then, the number of nosological entities and the knowledge of their pathophysiology and the genetic causes have been increasing continuously. According to the latest IUIS 2019 classification[2] of inborn errors of immunity, autoinflammatory diseases fall into two groups: VIIa and VIIb, and include 34 nosological entities divided into the following five categories:

- recurrent inflammation,
- systemic inflammation with urticaria rash,
- others,
- sterile inflammation of skin/bones/joints and
- type 1 interferonopathies.

Categories 1 and 2 include "classic" autoinflammatory syndromes, such as:

- Familial Mediterranean Fever (FMF),
- mevalonate kinase deficiency (MKV),
- TNF receptor-associated periodic syndrome (TRAPS)
- cryopyrin-associated periodic syndromes (CAPS).

In a number of autoinflammatory diseases, excessive inflammasome activation or dysregulation plays a key role in the pathophysiology. Inflammasomes are a type of intracellular multiprotein platform that triggers the production of IL-1β, which plays a predominant pathogenic role in the initiation of an inflammatory response. Therefore, from the point of view of the underlying mechanism, the diseases are considered inflammasomopathies. This translates into clinical practice since biologics that block IL-1 activity are used in these diseases. The first summaries about the undeniable benefits of treatment with Il-1 blockers based on many years of observation of patients with TRAPS, CAPS, MKD and FMF became the basis for creating treatment recommendations for these patients.[3,4,5] Pathological activation of inflammasomes results from defects in various genes and occurs through various, not always fully understood pathophysiological pathways.

In the last 20 years, both in Poland and in other countries, awareness of the existence of autoinflammatory diseases and consequently its recognition have been increasing. Patients present with symptoms related to many organs and seek help from many specialists, which frequently prolongs the time to proper diagnosis. The diagnostic investigations and treatment are typically conducted by immunologists and rheumatologists.

At present, data on European patients with autoinflammatory diseases are collected in several registries, Eurofever being the largest one. The Eurofever project was set up in 2008 by the Paediatric Rheumatology European

Society (PRES) Autoinflammatory Diseases' Working Group and was supported by the Executive Agency for Health and Consumers (EAHC). The Eurofever project established a close cooperation with AIDA – the international registry for adult autoinflammatory diseases. Data for the Eurofever registry are reported by 120 centres in 43 countries, which so far have collected information on more than 4000 patients with autoinflammatory diseases. According to a 2017 publication, 751 patients with classical monogenic SAIDs were reported to the Eurofever registry: 346 with FMF, 133 with CAPS, 114 with MKD and 158 diagnosed with TRAPS[6]

The first Polish center to begin to diagnose autoinflammatory diseases was the Department of Immunology of the Children's Memorial Health Institute in Warsaw – the first, genetically confirmed diagnosis of mevalonate kinase deficiency was established as early as in 1999. In 2012, the Department of Internal Medicine, Pulmonology, Allergy and Clinical Immunology of the Military Institute of Medicine in Warsaw began to operate, dedicated to adults. Initially, thanks to international collaboration, patients were assessed for genetic mutations at centers in France and the UK. In the first 10 years, the number of patients increased very slowly, while the last decade saw a substantial increase in the number of diagnoses established, especially the last five years. This results from the promotion of the knowledge of autoinflammatory diseases among rheumatologists, immunologists and other specialists. The availability of next-generation sequencing (NGS) was a breakthrough in the genetic testing, which also played a crucial role, greatly facilitating and accelerating diagnostic investigations. For several years, most patients have been undergoing genetic testing in Polish laboratories. The high price and the lack of reimbursement remain an unresolved problem, reducing the availability of such testing.

Methods

The aim of this study was to present the current situation in Poland in the diagnosis and treatment of patients with inflammasomopathies. The number of patients, both adults and children, with individual diagnoses of autoinflammatory diseases, including those treated with biological preparations blocking interleukin 1, was analyzed. An approximate comparison of the epidemiology of these diseases in Poland against other European countries and data from registries was made.

Results

Numbers of patients with autoinflammatory diseases reported to be treated in Poland

In Poland, there are still few centers with experience in the diagnosis and management of patients with autoinflammatory diseases. Pediatric patients are provided with treatment primarily at the Outpatient Clinic and Department of Immunology of Children's Memorial Health Institute (IPCZD) in Warsaw, while adults – at the Department of Internal Medicine, Pneumonology, Allergy and Clinical Immunology of the Military Institute of Medicine (WIM) in Warsaw. At present, most patients treated under the Congenital Autoinflammatory Diseases Treatment Programme are under the care of these centers. Numerical data from these centers account for the majority of monogenic autoinflammatory disease cases diagnosed in Poland.

Patient profiles (treatment initiation, course and duration)

TRAPS is a tumour necrosis factor (TNF) receptor-associated periodic syndrome that results from autosomal dominant pathogenic variants in the TNF super family receptor 1A (TNFRSF1A) gene. Patients with TRAPS are characterized by irregular but long-lasting (up to 2–3 weeks) episodes of fever. The episodes are frequently accompanied by erythematous, garland-like skin lesions on the trunk and limbs. The rash may be mistaken for parvovirus B19 infection and misdiagnosed as infectious erythema. The second distinguishing symptom is periorbital oedema reminding Glanzmann's sign in the course of mononucleosis. It is frequently accompanied by conjunctivitis. Fever may be accompanied by gastrointestinal symptoms such as abdominal pain and – less frequently – vomiting and diarrhea. The risk of AA amyloidosis in untreated patients ranges from 10% to 25%. During exacerbation, the levels of acute phase reactants increase and may persist also during clinically asymptomatic period, accompanied by polyclonal gammapathy, which translates into an increased risk of AA amyloidosis. Interleukin 1-blockers are currently the first-line therapy. TNF blockers may also be effective, but due to the formation of anti-drug antibodies their effectiveness tends to decrease with long-term therapy. Relapses are treated with non-steroid ani-inflammatory drugs (NSAIDs) used on an as-needed basis and – less and less frequently – glucocorticosteroids. In 11 years (between November 2009 and January 2018), 226 patients with TRAPS from 18 centers in 11 countries were entered in the Eurofever registry.[7] All patients, except for two, came from European centres in: United Kingdom (100 patients), Italy (47), France (19), Germany (18), Spain (13), The Netherlands (6), Poland (6),

Russia (5), Ireland (4), Greece (2), the Czech Republic (2), Turkey (1) and Slovenia (1). The mean age of onset was 5.3 years, and 43 of 226 patients (19%) presented with symptoms only in adulthood. IL-1 blockers, namely anakinra and canakinumab, were the most widely used and most effective medicines. Over 85% of patients achieved complete clinical response: 87.5% (49/56) were treated with anakinra and 86.4% (19/22) – with canakinumab. No patient who received anti-IL-1 treatment developed AA amyloidosis and seven women with a history of inability to get pregnant gave birth to a child. Etanercept was administered to 26 of 88 patients (30%); it proved less effective (< 16% of complete responses) and was discontinued in 17 of 26 patients (65%). Other biologics (rituximab, tocilizumab, and adalimumab) were used in rare cases and failed to achieve the expected benefits. The most important conclusion of the paper was the demonstration that anti-IL-1 biologics are the best available maintenance therapy for patients with TRAPS. The excellent therapeutic effect of the anakinra drug was also presents in Gattorno study, when patients were treated continuously with this drug and did not experience any disease-related clinical manifestations or any increase in acute-phase reactions.[8]

According to unpublished data, in Poland the diagnosis of TRAPS has been established and genetically confirmed in at least 24 patients. TRAPS has been diagnosed in 17 children at ≤ 18 years of age from 14 families and in 7 adults. Most of them are currently (as at February 2021) treated with anakinra: 14 children and all adults. Three of the seven adults developed a complications, namely renal AA amyloidosis. Only one pediatric patient (a female) presents with recurrent autoinflammation despite continued treatment with Kineret. As to other patients, we have been observing clinical remission, normalization of laboratory inflammatory markers and arrested kidney damage progression.

Given TRAPS prevalence in other countries, it is estimated that not more than 30% of all patients affected by the disease have been diagnosed in Poland. In Germany, 20 cases of TRAPS were reported in a 2009 publication and it was estimated that 6–10 cases were diagnosed in children at < 16 years old every year.[9] Therefore, it can be estimated that in 2020 the number of patients in Germany must have exceeded 100, which is about 1.2 cases per million. Regrettably, the number of cases entered in the Eurofever registry is much lower (only 18), which suggests problems with data reporting. For comparison, 100 patients were reported in the UK, which corresponds to 1.5 per million. On the basis of these simple calculations, we can expect at least 50–60 patients in Poland. The actual number of cases is probably even higher because in other countries not all patients are diagnosed either.

Cryopyrin-associated periodic syndromes (CAPS): FCAS, MWS and NOMID/CINCA are three diseases inherited as dominant traits associated with mutations in one NLRP3 gene (formerly known as cryopyrin). FACS - familial cold-induced autoinflammatory syndrome is characterized by the mildest phenotype. Irregular episodes, provoked by sudden changes in ambient temperature or cold, usually last for a short period of time, from several to 24 hours. After a challenge, within 30 minutes to six hours, patients present with generalized urticaria, chills and increased body temperature, often with arthralgia. More regular episodes are observed in Muckle-Wells syndrome (MWS), which last longer and are accompanied by stealthily progressive sensorineural hearing loss caused by chronic otitis media. The most serious phenotype manifested immediately after birth by patients with neonatal-onset multisystem inflammatory disease (NOMID) or chronic infantile neurological cutaneous and articular (CINCA) syndrome. NOMID/CINCA is characterized by almost permanent skin rash, fever and the development of destructive arthritis, frequently with massive hypertrophy of articular cartilage. Lesions within the central nervous system develop: chronic aseptic meningitis, sensorineural deafness, macular oedema, optic nerve atrophy, choroiditis and mental retardation. Approximately half of the patients experience relapses while the other half develop chronic inflammation.

CAPS usually occurs in the first year of life: the median age of first symptom onset is 0.8 years (0.1–5). Late forms are also known, which manifest in adulthood, as late as between the fourth and sixth decade of life. The median delay between the symptom onset and diagnosis is 1.4 years (0.2–8.9) The diagnosis is substantially delayed especially in the case of mild phenotypes (median age: 23.3 years) compared with more severe CAPS phenotypes.[4]

CAPS treatment with Il-1 blockers has been shown effective. Over ten-year safety data for IL-1 inhibitors use in CAPS are available. Standardized monitoring of disease activity and individually adjusted dosage offer hope for excellent control of the disease and its long-term complications. The Kuemmerle-Deschner et al. study assessed 68 patients with CAPS; median patient age was 25 years, the study involved 27 (40%) children, and median follow-up was 28 months. Overall, complete response (CR) was achieved in 72% patients with CAPS, with the rates significantly lower in the case of severe phenotypes (14%) compared with mild phenotypes (79%). Only 53% of patients achieved CR with the standard dose of canakinumab. Dose escalation was required more frequently in children (56%) than in adults (22%).

Patients with a severe clinical phenotype, especially in the first years of life, require higher doses calculated according to body weight to achieve remission.[5]

In patients with CAPS, a single dose of canakinumab may achieve rapid clinical and biochemical improvement within the first 24 hours of administration. In a 48-week double-blind, placebo-controlled, randomized study, 35 patients with CAPS treated with canakinumab achieved a complete clinical and biochemical response (CR) of 97%.[6]

As for anakinra, the typical dosage ranges from 1–2 mg/kg/day for patients with FCAS to 10 mg/kg/day for patients with NOMID/CINCA. Anakinra penetration into the CNS appears to be better, therefore it may be the treatment of choice in cases of aseptic meningitis.[7] Most CAPS patients require continuous therapy, and on-demand therapy is recommended only for patients with low disease activity.

Currently, in the pediatric population biological treatment with anakinra in the presence of cryopyrinopathy is being provided to eight patients, including four with evidence of pathogenic changes in the NLPR3 gene. In the adult population, the diagnosis was genetically confirmed in 12 patients, 11 of which are still being treated; one patient died from multiorgan AA amyloidosis. It is worth bearing in mind that approximately 40% of patients with clinically confirmed most severe cryopirinopathy, namely NOMID/CINCA syndrome, have no mutations in the NLRP3 gene. In a large percentage of these patients, further genetic testing with "deep sequencing" (next-generation sequencing [NGS]-based methods with greater depth) allows to detect somatic NLRP3 mosaicism, although such tests are not routinely performed in genetic testing.

Schnitzler syndrome is polygenic autoinflammatory syndrome which shares clinical similarity with CAPS. It is characterized by recurrent urticaria, monoclonal gammapathy and chronic signs and symptoms of inflammation. Similarity to CAPS is also confirmed by a very good response to treatment with IL-1β blockers. Currently, five adult patients with Schnitzler syndrome are successfully treated with anakinra in an internal medicine center.

Given the data from other countries, the number of patients with CAPS treated in Poland is very low. The prevalence of CAPS is estimated at 2.7–5.5 per million but the actual number may be higher, given the difficulties in diagnostic investigations and the establishment of correct diagnosis.[10] It appears that CAPS phenotypes differ in terms of the incidence and prevalence worldwide. CAPS has been reported on almost every continent and its geographic distribution may be affected by external factors such as the weather. Patients with FCAS may avoid exacerbations by avoiding exposure to cold, which is why they would prefer to live in a milder climate. In Europe, moderate MWS appears to be the most common CAPS phenotype.

It can be expected that the actual number of Polish patients oscillates between 100 and 200, which means that no more than 10–20% of cases have been diagnosed. This is highly concerning as untreated cryopyrinopathies are associated with a high risk of irreversible damage, including hearing loss, damage to the visual and motor systems and a high risk of AA amyloidosis.

Mevalonate kinase deficiency (MKD) is a mevalonate kinase defect resulting from mutations in the MVK gene, combining features of immune and metabolic diseases. Depending on the residual activity of the enzyme or its complete deficiency, variability of the severity and spectrum of manifestations has been observed, from a milder form (previously referred to as hyper-IgD syndrome) to severe mevalonate acidosis. Patients with the recurrent form suffer from recurrent episodes of fever, frequently accompanied by non-specific gastrointestinal disturbances such as abdominal pain, vomiting, diarrhea, lymphadenopathy, aphthous stomatitis, arthralgia and skin lesions of different morphology. The episodes tend to recur every 4–6 weeks and last for a few days; their onset is observed as early as in the first years of life. The episodes may be provoked by protective vaccination and infection. Among other autoinflammatory diseases, MKD is distinguished by its metabolic component and consequently the use of urinary organic acid profile tested (by GCMS) in a sample collected during exacerbation to establish a diagnosis. Identification of mevalonate aciduria is a simple key to establish the diagnosis, which can subsequently be confirmed by genetic testing. Severe forms of mevalonate acidosis result in progressive neurological problems such as arrested psychomotor development, ataxia or even epilepsy and almost constant elevation of inflammatory markers.

Macrophage activation syndrome, amyloidosis, joint contractures, liver dysfunction and abdominal adhesions may also develop. The disease typically occurs after six months of age and rarely after the age of five, but it may as well manifest during fetal development or in the first weeks after birth.[11]

In the most severe cases, hematopoietic stem cell transplantation is the treatment of choice and it has been successfully performed in two Polish patients with MKD. In the treatment of relapsed autoinflammatory condition biologics are used, mainly IL-1 and IL-6 blockers, but not all patients achieve symptom remission. The CLUSTER study evaluated the use of canakinumab in 72 patients at over two years of age (a double-blind, placebo-controlled study). CR was achieved in 35% of patients receiving 150 mg, and after dose escalation to 300 mg, the clinical effect was satisfactory in more than half of the patients (57%). Importantly, all the other patients achieved reduction in the severity and frequency of recurrences, with a significant improvement in the quality of life.[12]

The outcomes of anakinra treatment in several observational trials seem to be slightly worse, but it definitely is a therapeutic option and, interestingly, it can more easily be used 'on demand', i.e. only periodically, when autoinflammatory condition recurs.

At IPCZD, between 1999 and 2020 mevalonate kinase deficiency was diagnosed in seven patients. One female, who had been diagnosed as an adult in London, started treatment after kidney transplantation due to AA amyloidosis in internal medicine center in Gdańsk. Anakinra allows to control the disease symptoms while preventing AA amyloidosis recurrence in the kidney graft. Two patients with severe mevalonate acidosis were treated with anakinra but only partial relief of clinical symptoms was achieved. They underwent hematopoietic stem cell transplantation, which allowed for treatment discontinuation and marked improvement in their clinical condition. Regrettably, since the therapy is not reimbursement, the remaining patients, with a less severe clinical course, did not receive chronic treatment with anakinra or canakinumab.

In Poland, the number of undiagnosed patients with MKD or other monogenic autoinflammatory syndromes is probably much higher.

There are three published reports, all concerning European populations, stating an estimated prevalence of MKD as ranging from 1.3/1,000,000 in the Eastern and Central European countries in children aged 0–19 years, through 5/1,000,000 in the overall population in the Netherlands to 6.2/1,000,000 (HIDS) in Germany in children at ≤ 16 years of age .

The discrepancy between the above calculations makes it difficult to estimate the actual number of patients in Poland – it may range from several dozen to as many as 200.

Familial Mediterranean Fever (FMF) is the longest known and best clinically characterized autoinflammatory syndrome endemic to the Mediterranean Sea region, primarily. It affects mainly Sephardic Jews, Armenians, Turks and Middle Eastern Arabs, where the prevalence may range from 1/2,000 to 1/1,000. FMF is classically an autosomal recessive disease caused by mutations in the MEFV gene. FMF symptoms are observed also in individuals with only one pathogen variant, i.e. autosomal dominant (AD) form. An abnormal protein, i.e. pyrin, an inflammasome component, is produced, which interferes with normal inflammatory response and cell apoptosis. It is characterized by 1–3-day episodes of fever with sterile inflammation of the serous membranes (peritoneum, pleura, pericardium), arthritis and erythema. Untreated forms are complicated by AA amyloidosis. In FMF, colchicine is the main and usually effective drug, which in 70% of patients allows control of clinical symptoms, leads to normalization of inflammatory markers and, first of all, successfully prevents the development of AA amyloidosis. IL-1 blockers are successfully used especially in colchicine-resistant patients. In Poland, atypical forms of FMF are often diagnosed in patients with only one pathogenic variant in the MEFV gene. Eleven pediatric patients are under the care of IPCZD (unpublished data). Due to inefficacy of the first-line treatment, i.e. colchicine, it was decided to initiate biological treatment with anakinra in three of them. The patients experienced severe symptoms of recurrent pericardial and pleural effusions. All have achieved a good clinical response to the IL1 blocker. Of the adult patients, three are treated with colchicine, with very good tolerability and outcomes. One Armenian female patient requires the use of anakinra as an add-on to the maximum tolerated doses of colchicine (up to 3 mg/d) due to AA amyloidosis with renal involvement.

Patients with atypical FMF are likely to remain undiagnosed among patients under the care of cardiologists – due to recurrent exudative pericarditis or pulmonologists – due to recurrent exudative pleuritis, or gastrologists – due to non-specific gastrointestinal disturbances or suspected inflammatory bowel disease.

Interleukin-1 inhibitors

IL-1 blockers have been shown clinically effective in the treatment of inflammasomopathies.

Currently, four IL-1 blocking biologics are available. Two of them, namely anakinra and canakinumab, have been approved for clinical use in Europe and the US, whereas rilonacept and gevocizumab are approved only in the US.

The first step to initiate an inflammatory response is the binding of interleukin 1 with IL-1 receptor type 1 (IL-1R1) and adaptor protein IL-1RAcP in order to trigger signal transduction. The recombinant human IL-1R1 antagonist anakinra directly competes with IL-1 for binding to IL-1R1, blocking the biological activity of IL-1, both IL-1α and IL-1β of the IL-1 family. In contrast, human monoclonal IgG1 antibody canakinumab selectively neutralizes IL-1β and inhibits its binding to IL-1R. Basic differences in the pharmacokinetics of anakinra and canakinumab are presented in **Figure 1**.

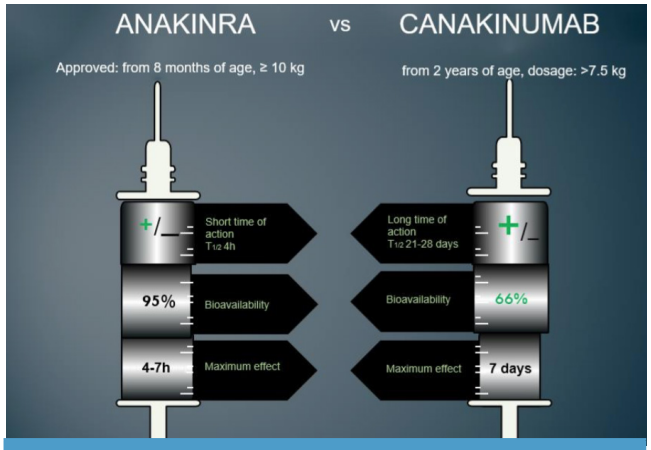

Figure 1. Basic differences in the pharmacokinetics of anakinra and canakinumab.

Canakinumab and anakinra differ in the duration of action and, consequently, dosing regimen: daily subcutaneous injections in the case of anakinra and administration every eight weeks in the case of canakinumab (half-lives: 4 hours vs 21–28 days). Infrequent administration of canakinumab has no doubt a favorable effect on compliance and is more convenient for patients. The short duration of anakinra action is important in the event of adverse reactions or a clinical situation in which the blocking of interleukin 1 may be detrimental to the patient's health, e.g. a serious infection.

The maximum therapeutic effect is achieved after several (4–7) hours in the case of anakinra and seven days in the case of canakinumab. Therefore, if a rapid onset of action and therapeutic effect assessment are needed as soon as possible, a short-acting blocker may prove better. In practice, anakinra is preferred at the beginning of treatment, especially in patients in whom definitive diagnosis has not been established or who receive it off-label (for indications other than the ones listed in the SmPC), on the basis of expertise. In the case of short-acting drugs used in both pediatric and adult populations, the dosage may be more readily selected and adjusted to disease activity.

Canakinumab efficacy in CAPS is best documented in numerous studies (1 RCT/5 non-RCTs/29 observational studies).

Complete clinical response was achieved in 78–100% of patients, with the remaining 22% achieving partial improvement in terms of severity and frequency of autoinflammatory condition recurrence. Treatment achieves remission of symptoms of both milder forms (FCAS, MWS) and severe forms (NOMID/CINCA), with dramatic effects not only on rash and acute-phase proteins but also on aseptic meningitis and cochleitis, which often lead to severe disability.[12,13] Also in TRAPS, MKD and FMF refractory to colchicine major therapeutic benefits, i.e. complete remission or significant relief of symptoms, are achieved, which translates into improved quality of life.

On the basis of studies conducted so far, mainly the CLUSTER study referred to above, recommendations for the use of individual products were developed, with the strongest recommendation for the use of canakinumab in CAPS, TRAPS and MKD, which was classified as 1B.[14]

Canakinumab has a broader range of approved indications according to the SmPC, which includes TRAPS, MKD, FMF and gouty arthritis, in addition to CAPS and sJIA.

Discussion

Do Polish patients receive optimal treatment?

By 2017, Polish patients did not have access to reimbursed treatment with IL-1 blockers.

Such therapy was provided to 12 pediatric patients, with 100% costs covered by parents, and two adult patients – one with complicated CAPS and one with TRAPS, with the consent of the National Health Fund (NFZ). The breakthrough came in October 2017 with the launch of the Congenital Autoinflammatory Syndromes Treatment Programme, reimbursed by the Ministry of Health and coordinated by the Autoinflammatory Diseases Section of the Rare Diseases Team. As part of the programme, anakinra is currently reimbursed for use in the indications listed in Table 1. In December 2020, the provision concerning eligibility criteria for the programme was modified to include "other IL-1-mediated autoinflammatory syndromes" as an indication for use. In December 2020, the provision concerning eligibility criteria for the programme has also been modified to include TRAPS and other IL-1-mediated autoinflammatory syndromes.

Table 1. Indications for patient eligibility to Congenital Autoinflammatory Syndromes Treatment Programme

a)	Cryopyrin-Associated Periodic Syndrome – CAPS: a. NOMID (Neonatal-Onset Multisystem InflammatoryDisease); CINCA (Chronic Infantile Neurological, Cutaneous, Articular Syndrome) b. MWS (Muckle-Wells Syndrome) c. FCAS (Familial Cold Autoinflammatory Syndrome)
b)	Other inborn autoinflammatory syndromes: a. TRAPS and other IL-1 -mediated autoinflammatory syndromes b. FMF, after unsuccessful treatment with the maximum tolerated dose of colchicine
c)	Polygenic IL-1 -mediated autoinflammatory syndromes a. Schnitzler syndrome
d)	Secondary amyloidosis in course of autoinflammatory syndrome

In the first year of programme operation, 24 patients were

enrolled – 13 children and 11 adults.

In the subsequent two years, the number of patients treated sharply increased to 56 in February 2021. As for the pediatric population, treatment is provided to 14 patients with TRAPS, eight patients with CAPS and three patients with FMF.

There are many clinical situations in which treatment is switched from canakinumab to anakinra or from anakinra to canakinumab. Ths most common reasons for changes in treatment with IL-1 blockers are: local reactions, non-compliance, partial response to treatment, pregnancy .

In pediatric practice, the possibility of using longer-acting canakinumab is vitally important due to a significantly lower number of unpleasant injections (once daily vs once every eight weeks) compared with anakinra. Less frequent drug administration tends to have a positive effect on compliance. Non-compliance is one of the primary causes of failure of chronic illness treatment. In the case of younger children, daily subcutaneous injections prose a major challenge to the parents and cause huge stress in the child, which may affect the course of autoinflammatory disease being a known trigger for immune reactions. There are some situations, such as going on holiday, in which the child could spend time with his peers but cannot do it because the parents cannot administer the drug. The short duration of anakinra action (about 24 hours) has some advantages, too. For example, in the presence of temporary contraindications for drug administration. The drug may be discontinued for any number of days and resumed at any time. In the case of a long-acting drug, its therapeutic concentration is maintained for eight weeks and after administration its effect cannot be reversed. Anakinra dosage may be modified easily, especially at the beginning of treatment, and its clinical effects may be observed. In practice, we often recommend that the dose be increased on an as-needed basis (even twice, for a few days) during a relapse. This applies to partial responders, e.g. patients with TRAPS. According to Kuemmerle-Deschner et al., treatment is switched from anakinra to canakinumab definitely more frequently than the other way round (11 vs 3). The most common reasons for anakinra discontinuation were as follows: the need for daily injections, injection site reactions, painful injections and the lack of or poor response to treatment. Switching to canakinumab occurred in a pregnant female, and also due to adverse reactions or lack of efficacy. All types of autoinflammatory syndromes have a negative impact on the quality of life of patients and there is a need for effective and reimbursable treatment of these syndromes. As in other European countries, physicians and patients should have the option to choose an optimal, individually tailored therapy. Considering that so far relatively few patients with cryopyrinopathies are diagnosed in Poland and that these syndromes are ultra-rare diseases (occurring with a frequency of <1 case per 50,000 people), unfortunately patients are in the area of financing that does not raise understanding among decision makers. Both interleukin-1 blockers should be available and reimbursed for both paediatric and adult patients. Taking into consideration the aspects of treatment efficacy and safety as well as the patient's quality of life and preferences is of central important because most patients require continued, systematic and most likely lifelong treatment.

Conclusions

The diagnosis of autoinflammatory diseases in Poland is constantly improving, but still the majority of patients remain undetected.

The introduction of reimbursed treatment with interleukin-1 blockers dramatically improved the quality of life of patients with inflammasomopathies.

Access to a broader spectrum of biological agents for the treatment of congenital autoinflammatory syndromes is expected.

Conflict of interest

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