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Case of Using the Inhibitor of Interleukin 1 Canacinumab in Patients with Auto Inflammatory Diseases

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The main inflammation mediator for many autoinflammatory diseases (periodic fever syndromes, PFS) is interleukin 1β (IL 1β). Cryopyrin associated periodic syndromes (CAPS) became first diseases for which the effectiveness of inhibitors IL 1 was shown with a high degree of substantiality. Canakinumab (fully human monoclonal antibodies to IL 1β) since 2011 is registered in the Russian Federation as a treatment for CAPS. Currently, there are studies evaluating the efficacy and tolerability of IL 1 inhibitor in patients with other PFS. Accumulated practical experience and some randomized controlled studies demonstrate the successful use of IL 1 inhibitor in colchicine-resistant patients in cases of familial Mediterranean fever with the blockage of inflammatory attacks and reducing acute-phase activity, as well as in patients with other monogenic (TRAPS, HIDS, and others) and multifactorial pathologies (systemic juvenile arthritis, Still's disease in adults, gout, etc.). The use of IL 1 inhibitors, in particular of canakinumab, in patients with a variety of PFS, according to Russian and foreign studies, showed good tolerability and high efficacy in all patients, regardless of age. Thus, canakinumab, due to its therapeutic opportunities, has broad prospects in facilitating the disease, improving the survival, quality of life and overall prognosis.

Keywords: *cryopyrin associated periodic syndromes, periodic syndrome associated with mutation of the tumor necrosis factor receptor, treatment, canakinumab, IL 1 inhibitors.*

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Introduction

Autoinflammatory diseases and syndromes (periodic fever syndromes, PFS) are a group of diseases which are united by recurrent episodes of spontaneously occurring non-infectious inflammation of known genetic nature, associated with the activation of an innate immune response in the absence of autoantibodies and antigen-specific T cells [1]. P. Fietta indicates that the term "autoinflammation" was proposed by D. Kastner and J. O. Shea in the late twentieth century, and since then it has firmly established in the lexicon of doctors [2, 3].

Common features of this group of diseases are recurrent episodes of fever, polysystem and increase in acute-phase markers (ESR, CRP, and others). For most PFS, debut in childhood is typical, for many so is the debut in the first year and even in the first weeks of life. Most nosologies, currently attributed to the classic PFS, have a monogenic hereditary nature, i.e., they are caused by a pathological mutation of one specific gene, which is now transcribed. PFS are diseases of natural (congenital, antigen non-specific) immunity, the central mediator of which is interleukin (IL) 1β [4-6]. Thus, the activation of Toll-like receptors (or their intracellular functional analogues responsive to various damaging factors) causes inflammasome activation, which in its turn activates the procaspase-1. The active form - caspase-1 – transforms the inactive form of pro-IL 1β into active, and after stimulation of the P2X7 receptor, the active cytokine is released into the extracellular space. Thus, each of these stages is the "point of regulation" of IL 1β expression [4, 7, 8].

Initially, the PFS group consisted of few rare congenital monogenic diseases, the so-called periodic fevers with frequent involvement of the skin, serous membranes, mucous membranes, eyes, joints, lymph nodes, gastrointestinal tract, and nervous system. At present, the list of PFS is wide enough and is regularly updated with new nosologies - monogenic and multifactorial diseases (Table 1) – with a different mechanism of development, in which, possibly, the genetic defect is not set [1, 9].

Table 1. ***Clinical classification of hereditary and multifactorial autoinflammatory diseases [9]***

Clinical signs	**Hereditary PFS (gene, transmission path)**	**Multifactorial PFS**
Recurrent episodes of inflammation	*FMF* (MEFV, AR) *TRAPS* (TN FRSF1A, AD) Hyper IgD-syndrome *(MVK,* AR)	Marshall Syndrome Recurrent idiopathic pericarditis Mollaret syndrome (recurrent meningitis)
Systemic inflammation with urticarial rash	CINCA / NOMID *(NLRP3,* AD) Muckle Wells Syndrome / FCAS *(NLRP 3* AD) *FCAS2* (NLRP12, AD)	System JA Adult Still's disease Schnitzler syndrome
Sterile inflammation of skin / bones / joints	*PAPA* syndrome (CD2BP1, AD) *DIRA* syndrome (IL1RN, AR) *DITRA* syndrome (IL36RN, AR)	SAPHO Gout and pseudogout Spondyloarthropathy Reactive arthritis

	CRMO *(LPIN2,* AR) *CAMPS* syndrome (CARD14, AD)	Sweet's Syndrome Generalized pustular psoriasis Acrodermatitis
Panniculitis / lipodystrophy	Nakajo-Nishimura syndrome (*PSMB8* AR) *JMP* syndrome (*PSMB8*, AR) *CANDLE* syndrome (*PSMB8*, AR)	Neutrophilic panniculitis Erythema nodosum and panniculitis
Inflammatory bowel disease	Early onset of inflammatory bowel disease *(IL10, IL10RA, IL10RB)*	Crohn's Disease
Hemophagocytosis lymphohistiocytosis (FHL)	FHL 1 (unknown) FHL 2 *(PFR1* / perforin 1, AR) FHL 3 *(UNC13D* / Munc 13-4, AR) FHL 4 *(STX11* / syntaxin 11, AR) FHL 5 *(STXB2* / syntaxin binding protein, AR)	System JA - associated MAS Infection - associated MAS

Note: PFS - autoinflammatory diseases, blood pressure - autosomal dominant, AR - autosomal recessive, TRAPS - Tumor necrosis factor receptor-associated periodic syndrome; JA - juvenile arthritis, FMF - Familial Mediterranean fever, MAS - macrophage activation syndrome; FCAS - familial cold autoinflammatory syndrome; CRMO - chronic recurrent multifocal osteomyelitis, SAPHO - syndrome, including synovitis, acne, pustulosis, hyperostosis, osteitis.

The PFS problem has been studied for nearly half a century. Each of the PFS is characterized by the predominance and combination of certain symptoms, varying in severity, frequency and nature of the flow. The presence of acute-phase markers at increased levels during attacks is pathognomonic.

The accumulated clinical experience shows that most of the PFS have a severe course and a serious prognosis. Treating such patients is very difficult. Use of genetically engineered biological agents (GEBA) in the last decades led to a breakthrough in the treatment of PFS. According to several studies with a high validity level, it is possible to virtually eliminate manifestations of these syndromes, previously considered incurable and leading to permanent disability and death of the patient.

Today, a fundamentally new approach to the treatment is the use of drugs that block the function of the main cytokine IL 1 involved in the process of autoinflammation. Currently, the representatives of IL 1 inhibitors are anakinra (recombinant soluble IL 1 receptors antagonists), rilonacept (recombinant receptor fragment connected with an additional protein of receptor to IL 1 and an immunoglobulin G to IL 1) canakinumab (fully human monoclonal antibodies to IL 1β) (Table 2). Registration of these preparations is carried out only for cryopyrin associated periodical syndromes and for gout. However, attempts at prescribing them in various PFS are available. Other therapeutic options, that are at the stage of clinical trials, related to the suppression of IL 1 activity, are considered, including, for example, IL 1α neutralization, and inhibition of caspase-1 [9]. Accumulated practical experience and some randomized controlled

studies demonstrate the successful use of IL 1 inhibitor in colchicine-resistant patients with familial Mediterranean fever, which results in the blockage of inflammatory attacks and acute-phase activity reduction [9−11], as well as in patients with other monogenic (TRAPS, HIDS, Blau syndrome, PAPA, DITRA and others) and multifactorial (systemic juvenile arthritis, Still's disease in adults, Behcet's disease, Schnitzler syndrome, gout and pseudogout, CRMO, SAPHO, etc.) diseases [9].

Table 2. ***Genetically engineered biological agents that block the function of IL 1.***

The preparation	Anakinra	Rilonacept	Canakinumab
Type	Recombinant soluble antagonists of IL -1	Recombinant soluble receptors IL -1	Fully human monoclonal antibody to IL -1 β
Injection way	Subcutaneously	Subcutaneously	Subcutaneously
Dose	1 - 3 mg / kg (max 100mg)		2 - 4 mg / kg
Multiplicity of injection	Daily	1 per week	1 per 8 weeks
Register at CAPS	US FDA for CINCA / NOMID	02/2008, the US FDA for the treatment of CAPS (CAPS - FCAS or MWS in adults and children older than 12 years)	06. 2009, US FDA for FCAS and MWS in adults and children older than 4 years; EMEA for the treatment of all types of CAPS in **10.2009,** in Russia since 01.2011

Note: FDA- Food and Drug Administration, CAPS – cryopyrin associated periodic syndromes; CINCA / NOMID - Chronic Infantile Onset Neurologic Cutaneous Articular / Neonatal Onset Multisystem Inflammatory Disease; FCAS - Familial Cold Autoinflammatory Syndrome; MWS - Muckle - Wells Syndrome; EMEA - European Medicines Agency

CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES

Classic PFS example are the Cryopyrin-Associated Periodic Syndromes (CAPS), which are a group of rare autoinflammatory diseases, including Familial Cold Autoinflammatory Syndrome / Familial Cold Urticaria (FCAS / FCU); Muckle - Wells Syndrome (MWS), Chronic Infantile Onset Neurologic Cutaneous Articular / Neonatal Onset Multisystem Inflammatory Disease (CINCA / NOMID). The development of the above syndromes, actually representing a single disease with different severity of clinical manifestations, severity of the pathological process and outcome, is caused by a mutation of the *CIAS 1 / NLRP 3* gene, encoding cryopyrin protein [12-16].

Type of inheritance of the disease - autosomal dominant.

Clinical manifestations. Mutation is found in about 60% of patients with CAPS. The overall clinical picture of CAPS, except fever, includes the skin, neurological, ophthalmological and articular manifestations, which are characterized by an early onset (usually in the first year of life) [3, 16].

Fever - Episodic, recurrent or persistent.

Skin Syndrome is localized in different parts of the body and limbs urticaria rashes, which can migrate and disappear during the day, their intensity increases in the evening. Rash character is diverse: spotted, Separated popular, or discoid. The rash resembles the hives, but by the nature of morphological changes, it is not a true allergic [16].

Neurological symptomatology is caused by lesions of the central and peripheral nervous systems, is various in manifestations and severity depending on the form of CAPS, ranges from headaches, hearing loss, increased intracranial pressure prior to the development of meningitis [17]. Sensorineural hearing loss may develop in adolescence and adulthood, and progress to the extent of the disease.

Ophthalmic symptoms include conjunctivitis, uveitis, and sometimes swelling of the optic nerve and its atrophy.

Articular manifestations. There is a wide range of joint damage - from arthralgias to severe arthropathy (more characteristic for CINCA / NOMID) - with involvement of large joints, usually the knee, resulting in hypertrophy with joint deformity and functional impairment, which is based on progressive ossification of cartilage with the formation of calcifications in joints.

Renal function. Amyloidosis develops in 25% of patients with CAPS with the most frequent localization in the kidney, which is often a cause of death. This complication is causing the extremely unfavorable projections for patients with CAPS.

Mortality during adolescence in patients with CINCA/NOMID is about 20%, mainly due to the development of infectious complications or neurological disorders.

Treatment. For the treatment of patients with CAPS in previous years anti-inflammatory, antihistamine, traditional immunosuppressive and cytotoxic drugs (methotrexate, cyclosporine, azathioprine, and cyclophosphamide) were used; however, the results were disappointing. Some improvement was noted when using high-doses therapy with glucocorticoids and thalidomide [3, 12, 18]: they could to a certain extent alleviate the symptoms and even interrupt the attack, but did not change the course of the disease and the prognosis, which in patients with the MWS syndrome and especially with CINCA/NOMID was sad. In number of patients, the efficacy of etanercept against articular manifestations was demonstrated. However, it did not affect the rash, fever, and acute phase reactants [19].

Canakinumab in CAPS therapy. Since IL 1 plays central role in the pathogenesis of CAPS, its blockade is the main therapeutic option. The only possible for an official prescription to patients with CAPS in the Russian Federation currently is canakinumab (Ilaris, Novartis Pharma AG, Switzerland). In 2009, the product has been registered by Food and Drug Administration (FDA; USA) for the treatment of FCAS and MWS, EMEA from age of 4 years; in 2011 it was registered in Russia for the treatment of CAPS. The drug is injected

subcutaneously 1 time every 8 weeks. The dose for children older than 4 years with a body weight ≥ 15 kg and ≤40 kg is 2 mg/kg, with a weight of ≥ 7.5 kg and < 15 kg - 4 mg/kg. In patients, weighing ≥ 40 kg the drug injects subcutaneously at a dose of 150 mg.

Canakinumab binds to soluble IL 1β and neutralizes its biological functions - blocks the binding with IL 1 receptor. The level of IL 1β production in patients with CAPS is 5 times higher than that in healthypeople, and this causes significant increase in acute phase inflammatory markers (CRP, SAA) in the blood. Reduce in IL 1β level leads to normalization of indicators of inflammatory markers. Canakinumab does not bind and inactivate neither IL 1α, nor IL 1RA [9, 20, 21].

Randomized controlled studies on the use of canakinumab in patients with CAPS are not numerous [9, 20-27]. H. Lachmann et al. [23] published the results of a multicenter 48-week double-blind randomized research (third phase) on evaluating the effectiveness on canakinumab in patients with CAPS. Research consisted of 3 parts. In the first were included 35 pacients in age from 4 to 75 years with a body weight of 15 to 100 kg. At the first open stage by a single subcutaneous injection, patients with weigh t> 40 kg were given 150 mg/kg, ≤40 kg - 2 mg/kg. The effect was assessed on the 15th day, and after 8 weeks, after which patients were included into the next phase of the study, taking canakinumab at 150 mg (n = 15) or placebo (n = 16) every 8 weeks up to 24th week. Upon completion of the second phase or during exacerbation, the patients (n = 31) in the third open phase took twice the dose compared to the first stage. In all patients in the first open phase, all symptoms were cropped during 24 hours, 97% had a complete response by the 15-th day after injection. On completion of the initial phase, residuary patients (n = 31) were randomized into the second phase: in 15 patients treated with canakinumab, clinical and laboratory remission is fixed, in 13 of the placebo group - exacerbation within 100 days, and increase in the level of inflammatory markers. By the end of the study, 30 patients of the 31 had absent or minimal signs of activity. Rash disappeared in 94%. The production of antibodies to the canakinumab was not found.

In the J. B. Kuemmerle-Deschner study (third phase), canakinumab was given to 166 adults and children with CAPS [24]. Complete response was obtained in 78% of patients within 8 days. In patients with incomplete response and residual symptoms (24.1%), among which dominated children and patients with severe CAPS phenotype, the dose was increased to 600 mg, or 8 mg/kg, in some patients the interval between injections was cut. During prolonged observation, there were no noted exacerbations in 90% of patients.

In R. Goldbach-Mansky et al. research, 6 patients aged 11-34 years with CINCA/NOMID received the drug at 150 mg (2 mg/kg) or 300 mg (4 mg/kg) every 4-8 weeks [25]. If necessary, doses were increased to 600 mg (8 mg/kg). In 5 patients remission was observed, in accordance with the evaluation of the patient. However, the continuing increase in CRP level in 1, persisting sleukocytosis in the cerebrospinal fluid in 5, and the progression of hearing loss in 1 patient led to the increase of dose to 8 mg/kg in all patients. Tolerability in both adults and children was good.

About the need for regulation and increasing doses of canakinumab in severe patients with CINCA/NOMID also reports R. Caorsi [26]. Published results on the application of canakinumab in 13 patients with CAPS demonstrate the need to increase dose and to reduce the intervals between injections.

As reference points for monitoring, except general inflammatory manifestations, serve an assessment of the dynamics of eye disorders, audiogram, kidney function; magnetic resonance imaging of the brain. Efficiency of canakinumab in terms of the impact on hearing loss was studied in 63 patients [24]: improvement was seen in 13, as well as the absence of progression of hearing loss (in 29) and of complaints of hearing loss in the period of observation. Unfortunately, data on the canakinumab impact on severe arthropathy, ocular and central nervous system manifestations, as well as on the reverse development of amyloidosis and other symptoms, are extremely few and inconclusive.

The results of the research on the canakinumab use distant safety are demonstrated in the H. Hoffman et al. work in 234 patients [27]: adverse events occurred in 27.8%. The most common were upper respiratory tract infections (13.2%) urinary tract infections. Serious adverse effects were registered in 8.5%.

TRAPS-SYNDROME

TRAPS (TNF Receptor-Associated Periodic Syndrome) is a periodic syndrome associated with mutation of the tumor necrosis factor receptor – it also is a classic representative of PFS. It is noteworthy, that in the basis of the autoinflammation concept, formulated by eminent American researcher D. L. Kastner et al., laid information about exactly TRAPS-syndrome [28, 29]. Initially TRAPS was described in 1982 by the example of a large Irish family and was called a familial Irish fever similar to the familial Mediterranean fever [29-32]. In the futire cases of TRAPS have been identified in many different ethnic groups, both European and non-European (African Americans, Puerto Ricans, Arabs)[3, 33].

TRAPS is monogenic disease, induced by mutation of *TNFRSF1A gene,* located on the short arm of 12 chromosome (12p13) [30]. Today there are more than 100 *TNFRSF1A* mutations associated with the development of TRAPS [28, 33]. They are located in those areas of the gene that encodes the extracellular portion of the receptor molecule. The vast majority of mutations is located in 2, 3, 4 exons, encoding the first two N-terminal located cysteine-enriched domains (CRD 1 and CRD 2) of 55 kDa receptor molecule.

Type of inheritance - dominant autosomal. Tumor necrosis factor (TNF) α is the most important proinflammatory cytokine produced mainly by monocytes/macrophages, lymphocytes, NK-cells, and polymorphonuclear leukocytes [3, 32].

Pathogenesis. The pathogenesis mechanisms of TRAPS are not fully disclosed. The following are the leading hypothesis [34-36]:

- mutations lead to a violation of metalloproteinase-dependent cleavage of the receptor molecule and its shedding from the cell surface, resulting in a reduction of pTNF - natural antagonist of ligand molecule – content in biological fluids, especially in

serum. Such mechanism was experimentally demonstrated for some mutations (C33Y, T50M, C52F) [34−36];

- reduction of TNF α-induced apoptosis of neutrophils and fibroblasts (for mutations affecting cysteine residues of the receptor molecule), as well as violations of motion of the molecule receptor I from cytoplasm to the cell surface.

Note that the last hypothesis becomes a dominating one. Demonstrated that the mutant molecules pTNF55 with modified stacking of peptide chain accumulates in the endoplasmic reticulum, is perceived as an internal factor of damage, i.e., as proinflammatory stimulus, leads to violations of mitochondrial functions increasing the production of active oxygen forms, and also to reducing the sensitivity to external natural immunity stimuluses (e.g., to lipopolysaccharides of gram negative bacteria), resulting in overproduction of other proinflammatory cytokines [34, 36].

The age of disease inception varies from 2 weeks to 53 years of life, but most often the debut develops at the average age of 3 years. Cases of illness onset in adulthood are not uncommon, which distinguishes TRAPS of most others PFS. Fever attacks are characterized by significant duration - from 1-3 to 5-6 weeks, the average interval between attacks - 21 days, but it can vary within wide limits (there are cases of short intervals - 2-3 days) [3, 10, 12, 16 , 32, 34].

Clinical manifestations. The attacks are characterized by febrile fevers, accompanied with rash (erythematous, maculopapular, annular, urticarial), conjunctivitis, periorbital erythema with edema (often single-direction), and sometimes with uveitis, myalgia, arthralgia, and abdominal pain. In rare cases, non-erosive arthritis is noted, touching usually large joints. One of the characterizing distinguish clinical manifestations of TRAPS is centrifugal myalgia, which is the based on fasciitis, identified with the help of magnetic resonance imaging. Frequently, over the myalgia area, locates the spreading centrifugal erythema [3, 10, 34, 37]. The most serious complication of TRAPS - development of renal amyloidosis - is noted in 24% of patients with mutations affecting cysteine residues, and only in 2% of patients with different type of mutations [34, 37, 38].

Treatment. Prior to the GEBA era, in the treatment of TRAPS for the attack blockage, non-steroidal anti-inflammatory drugs and glucocorticoids in doses greater than 20 mg per day were used [3, 32]. Such approach is still allowed for mild cases, rare attacks and the presence of mutations, not affecting the cysteine residues in the protein molecule, when the risk of amyloidosis is low. However, it must be remembered that this therapy is, in fact, symptomatic and does not affect the prognosis of the disease. Effect of colchicine in TRAPS is significantly lower than in familial Mediterranean fever; when using a drug in patients with TRAPS significant amount of therapeutic failures was noted, but at the same time, there are evidences that of its effectiveness in some patients [3, 39]. With the advent of GEBA, the first drugs that have been used for the treatment of TRAPS were TNF α-inhibitors. Drugs that are monoclonal antibodies to TNF α (infliximab, adalimumab), showed unsatisfactory efficacy and even served the cause of exacerbation of symptomatology [37]. Use of the drug based on recombinant

receptor (etanercept) was much more successful, and resulted in state improvement or remission of the disease in most patients, but in the treatment process a secondary ineffectiveness developed (average in 3.3 years) [37, 40, 41]. The most effective among GEBA in patients with TRAPS were IL 1inhibitors [11,29, 37]. They have led, on the one hand, to quick relief of inflammatory manifestations, and to less frequent attacks, and on the other hand - to prevention and even regression of amyloidosis [37]. The greatest experience in the world has accumulated on the drug anakinra, which is the recombinant receptor antagonists to IL 1. Most patients with initially successful etanercept use, by virtue of its secondary inefficiency subsequently demanded on transfer to IL 1-inhibitor anakinra. Primary or secondary inefficiency in patients with TRAPS rarely became a reason for the cancellation of this drug. There are individual data about good results when using tocilizumab in patients with TRAPS [33, 37]. The experience of successful use of monoclonal antibodies to IL 1β - canakinumab, one advantage of which is the infection 1 time per 8 weeks (unlike the daily injections of anakinra) is accumulating [11, 29, 33, 37, 40-43]. Results of 33-month open research evaluating the efficacy and safety of canakinumab in 20 patients with TRAPS, published by M. Gattorno et al. [42], showed the onset of clinical remission in all participants on the 15th day of the drug injection. It should be noted that after the drug cancelation, exacerbation of the disease developed in the period from 71.5 to 121.5 days, that is, the period of the disease symptoms absence has been long enough, that can probably serve as an occasion to discuss the multiplicity of injection in some patients. Adverse events occurred infrequently and were represented in the majority of pations as infections of the respiratory tract.

CLINICAL CASE

Canakinumab usage in patients with PFS in Russia is at the initial stages and is represented by single participants. This publication provides the experience Medical Genetic Research Centre of inhibitor IL 1 canakinumab usage in patients suffering from CAPS and TRAPS. The study included 7 patients with CAPS: 4 - with MWS, 2 - with CINCA/NOMID, and 1 - with TRAPS syndrome.

Characteristics of patients (table 3): 5 female patients aged from 3.5 to 41 year, 2 males, one of which is aged 9 years (TRAPS), and the other - 18 (with CINCA/NOMID). Two patients - daughter (18 years) and mother (41 years) - are a familial happening of MWS. The disease remoteness - from 3.5 to 33 years. In all the patients, the molecular genetic analysis of genes mutation is carried out. In 4 patients with MWS, identified mutations *NLRP3* gene (Thr436Ile и Thr438Ile, Thr350Met in mother and daughter); two patients with clinically significant phenotype CINCA/NOMID were negative for mutations. In TRAPS patient identified pHis51Tyr mutation. MVK mutations were found in none of them. All patients before prescribing canakinumab had some signs of active disease: rash (in 7); fever (in 7); ocular symptoms in form of conjuctivitis (in 3), uveitis (in 5); sensorineural hearing loss (in 2); articular manifestations (in 6), CNS lesions (in 2; in 1 - in the anamnesis); abdominal pain, vomiting in anamnesis (in 1 with TRAPS); the lag in physical development in patients with

CINCA/NOMID (in 1 with impaired intellectual development and cognitive function); improvement of acute-phase markers (in 7).

Table 3. ***Clinicogenetic characteristics of patients receiving canakinumab.***

Options	D.V., 3,5 years	K.YU., 6 years	M.T.18 years	M.V. 41 years	P.L, 9,5 years	B. A. 18 years	V.D. 9 years
Debut age	From birth	1 month	10 Months	7 years	From birth	From birth	6 Months
Diagnosis	MWS	MWS	MWS	MWS	CINCA / NOMID	CINCA / NOMID	TRAPS
Fever	+	+	+	+	+	+	+
Rash	+	+	+	+	+	+	+
Ocular symptoms	Conjunctivitis	-	Conjunctivitis, uveitis	Conjunctivitis	Stagnation of the optic nerve	Chorioretinitis, Partial atrophy of the optic nerve	-
Sensorineural hearing loss	**-**	**-**	**-**	**+**	**-**	**+**	**-**
Joints	Arthralgia / arthritis	-	Arthralgia / arthritis	Arthralgia / arthritis	Arthralgia / arthritis	Arthralgia / arthritis	Arthralgia
CNS	-	-	-	-		Hydrocephaly, multiple arachnoid cysts	Serous meningitis, convulsions
Other signs	-	-	-	-	Physical development delay	Physical / mental development delay	Abdominal pain, vomiting, pericarditis
Acute-phase markers	+	+	+	+	+	+	+
Mutation	Thr436Ile	Thr438Ile	Thr350Met	Thr350Met	No	No	pHis 51 Tyr
Treatment	**Response to treatment**						
A/B **GC** **NSAIDs**	No Effect No Effect No Effect	No effect No data No Effect	No Effect Incomplete No Effect	No Effect Incomplete No Effect	No Effect No data No Effect	No Effect No data No Effect	No Effect Incomplete No Effect

Note: A / B – antibacterial drugs; GC - glucocorticoids, NSAIDs - non-steroidal anti-inflammatory drugs

Concomitant therapy. One patient with MWS, and one - with TRAPS by the time of the study took glucocorticoids at 0.1 and 0.7 mg/kg per day, and the rest received NSAIDs symptomatically. During the previous years of the disease, almost all patients received some anti-rheumatic drugs, including glucocorticoids, azathioprine, cyclosporine A, colchicine and other, which did not have the desired effect. One patient with CINCA/NOMID was attempted to prescribe TNF-inhibitor adalimumab, which led to the deterioration. Canakinumab was

prescribed at a dose of 4 mg/kg for the weighing up to 15 kg, and 2 mg/kg – for the weighing more than 15 kg; it was injected subcutaneously every 8 weeks. To date, therapy is carried out for 1.5 years, maximum 10 injections are done.

Results. On the background of treatment with canakinumab, in all patients within a few days there was a significant clinical improvement: normalization of health, blockage of fever, disappearance of the rash (Fig.1), decrease in severity of lymphadenopathy and hepatosplenomegaly, blockage or decrease the severity of ocular symptomes, improvement of hearing (Fig. 2), decline in acute-phase markers, significant improvement of mood (Fig. 3-5). The effect of the same intensity was maintained in all the study participants during the whole observation period. Nevertheless, the level of acute-phase markers (CRP, ESR) in the heaviest patient with CINCA / NOMID with a long period of illness remained heightened. In two patients taken glucocorticoids, it was impossible to completely cancel them, herewith prior occurred manifestations of medical syndrome of Cushing disappeared. The tolerability of therapy was generally good. In two patients adverse events were registered: the girl with MWS had skin changes in the form of annular granuloma, which, after detailed examination, and eliminating all the possible causes, were regarded as manifestations of fungal infection (on the background of antifungal therapy, significantly improvement was noted, after which the temporary suspenssed canakinubaum therapy was continued). Patient TRAPS had recurrent furunculosis on the background of the first three canakinubaum injections, regarded as adverse events during the canakinubaum therapy (furunculosis responded to standard therapy and did not recur in the future). Other undesirable effects have not been identified. In the period of use of the drug in almost all children and adults, there were some euphoria, excitability and disinhibition, a significant increase in the emotional background. Such adverse events did not look unexpected, since abnormal weakness, fatigue, drowsiness and others are also associated with the overproduction of IL 1β.

Fig. 1. Dynamics of the skin changes during the canakinubaum treatment in patient with CINCA / NOMID before treatment

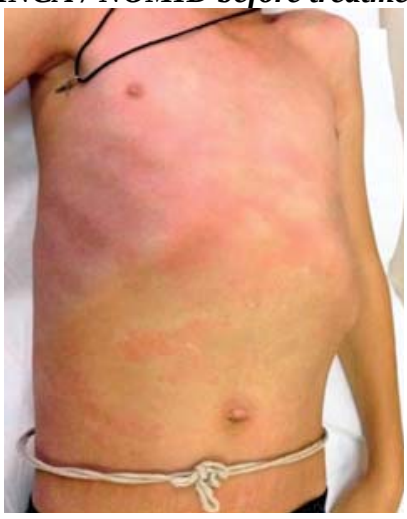


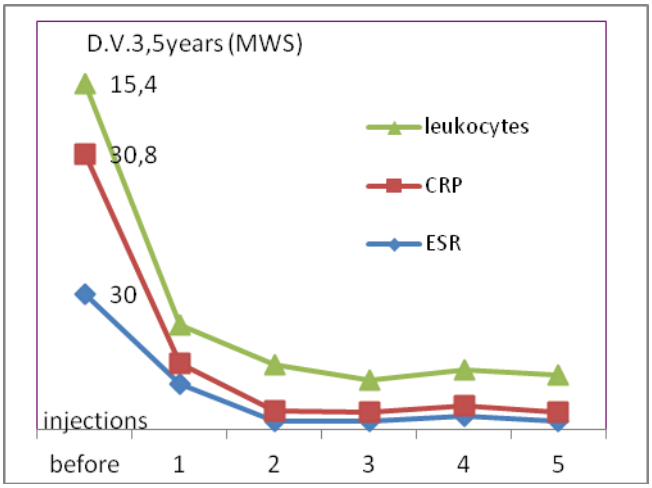
Fig. 2. Changes in the severity of sensorineural hearing loss during canakinubaum treatment in patient with CINCA / NOMID a) sensorineural hearing loss of 2 degree before the treatment; b) sensorineural hearing loss of 1 degree during therapy.

a)

b)

Fig. 3 a, b. Dynamics of laboratory markers of inflammation during the canakinumab treatment of patients with Muckle Wells Syndrome

a)



b)

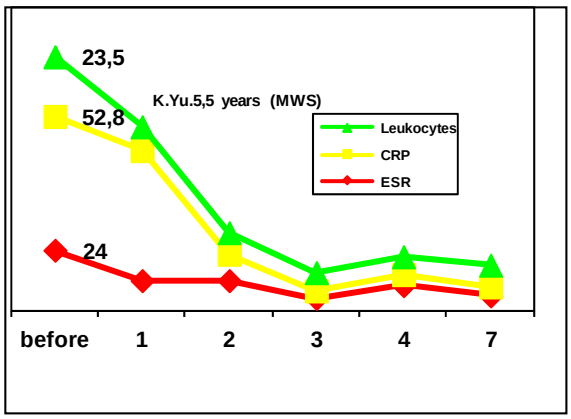
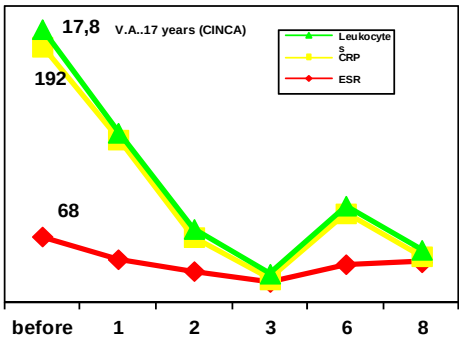
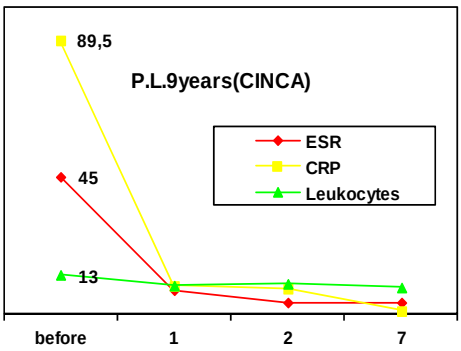


Fig. 4 a, b. Dynamics of laboratory markers of inflammation during the canakinumab treatment of patients with CINCA / NOMID



a)



b)

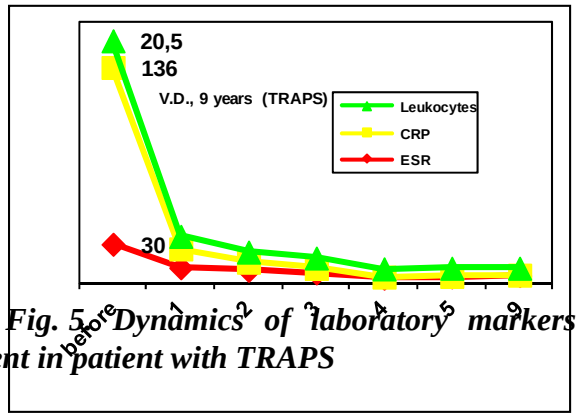


Fig. 5 Dynamics of laboratory markers of inflammation during canakinubaum treatment in patient with TRAPS

CONCLUSION

Thus, the little experience that the Centre possesses for canakinumab use in patients with CAPS and TRAPS showed a high efficacy and good tolerability. The decline in acute-phase markers was slower in the patient with CINCA/NOMID syndrome - the most severe CAPS representative. The results of treatment once again confirmed the concept of IL 1β role as a key factor in the pathogenesis of CAPS, as well as of other PFS. The effect of canakinumab can be assessed as excellent in all patients regardless of their age. No serious adverse events were

observed. The use of IL 1 inhibitors in patients with different variants of PFS has broad therapeutic potential in the prospects of alleviate the disease, improving the survival, quality of life and overall prognosis.

CONFLICT OF INTEREST

The authors have indicated they have no financial support / conflict of interest relevant to this article to disclose.

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