CLINICAL OBSERVATIONS

Biologic disease-modifying antirheumatic drugs in the treatment of major monogenic autoinflammatory diseases: literature review and clinical observation

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Autoinflammatory diseases (AIDs) are a heterogeneous group of rare genetically determined conditions, the main manifestations of which are episodes of fever in combination with other signs of systemic inflammation: skin rashes, musculoskeletal and neurological disorders, damage to the organs of vision, hearing, etc., as well as acute phase markers and the absence of autoantibodies. The use of biological therapy, especially inhibitors of interleukin 1 (iIL1), in most common monogenic AIDs (mAID) – FMF, TRAPS, HIDS/MKD, CAPS – has shown its high efficiency and led to significant progress in the treatment of these patients. Currently, iIL1 are the first-line drugs for mAIDs therapy, primarily CAPS. In the case of their ineffectiveness or intolerance in certain situations, other biologic disease-modifying antirheumatic drugs can also be used – inhibitors of tumor necrosis factor α and iIL6, but this issue needs further investigation.

The article describes a patient with mAID, in whom the diagnosis was made more than 40 years after the onset; administration of targeted therapy even in the late stages of the disease led to a significant improvement in many symptoms and quality of life.

Key words: *autoinflammatory diseases; FMF; CAPS; TRAPS; HIDS/MKD; biological therapy; interleukin 1 inhibitors.*
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Autoinflammatory diseases (AIDs) are a heterogeneous group of rare genetic disorders, the main manifestations of which are episodes of fever in combination with other signs of systemic inflammation: skin rashes, musculoskeletal, and neurological disorders, damage to the organs of vision, hearing, etc., as well as other clinical symptoms which frequently imitate rheumatic diseases. Indigenous signs of these conditions are as follows: markers of acute inflammation (increase in ESR, CRP, serum amyloid A (SAA) protein level, etc.), the absence of autoimmune, infectious, and other provoking factors, as well as autoantibodies and antigen-specific autoreactive cells, at least in the onset of the disease [1–5]. Both monogenic hereditary diseases (mAIDs) and polygenic hereditary diseases are distinguished among AIDs.

The first records about AIDs were reported about 20 years ago. Today, the subject of careful study, development of recommendations for diagnosis, management, targeted therapy are four main mAIDs or monogenic periodic fevers: Familial Mediterranean Fever (FMF), or periodic disease; a periodic syndrome associated with tumor necrosis factor receptor – TNF (Tumor necrosis factor Receptor-Associated Periodic Fever Syndrome, TRAPS); Hyper-Immunoglobulinemia D-syndrome/Mevalonate Kinase Deficiency (HIDS/MKD); Cryopyrin-Associated Periodic Syndromes (CAPS) [2–11].

AIDs is a chronic condition that significantly affects the life quality of a patient due to amyloidosis, organ damage, negative effects on the physical component of health, fertility, and childbirth, family and professional life. In addition, any rare disease is inevitably followed by social and psychological issues. It is extremely difficult for a patient to start a check-up with so-called "specialists for adults" who are not always fully aware of these rare disorders and hence mAIDs patients are observed by pediatricians for a protracted period of time.

MAIDs therapy mainly aims to control or suppress inflammation, prevent complications and organ damage, improve the quality of life for patients who suffer from chronic inflammation. Before the age of application of genetically engineered biological drugs (GEBD) in rheumatology, the management of patients with mAIDs was very difficult. The use of various symptomatic products, in particular, non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, and antibacterial products appeared to be ineffective. Although glucocorticoids (GCs) prescription improves the condition, the full response to the treatment is not reported. What is more, after the withdrawal from GCs or when the dose is decreased, disease recurrence is reported, and with prolonged use, well-known complications of such therapy occur. The only really significant indication for the use of GCs is febrile myalgia syndrome in FMF. Synthetic basic anti-inflammatory drugs (methotrexate, sulfasalazine, cyclosporine A, etc.) also do not provide the desired result [12–16].

Taking into account the pathogenesis of main mAIDs and the key role of the pro-inflammatory cytokine autoinflammation, i.e. interleukin (IL)1I inflammation, IL-1 inhibitors have become one of the first drugs used to treat mAIDs. Since 2009, several multicenter double-blind placebo-controlled and pilot studies, including routine clinical practice, have demonstrated with a high degree of evidence the efficacy and good tolerability of IL-1 inhibitor canakinumab in the treatment of CAPS [17–27]. In the Russian Federation, this drug was authorized for the CAPS indication in 2013 (See the Table).

Although another type of IL-1 inhibitor, anakinra, is used in the world, in Russia, it was authorized only in February 2021 for

Use of IL-1 Inhibitor canakinumab in mAIDs Patients

Parameter	FDA	EMA	Russian Federation
Indication	**CAPS (FCAS, MWS)**	**CAPS (FCA, MWS, CINCA/NOMID)**	**CAPS (FCA, MWS, CINCA/NOMID)**
Registration date	June 17, 2009	November 2009	March 5, 2013
Age / body weight	≥4 y.o./more than 15 kg	≥2 y.o./more than 7.5 kg	≥2 y.o./more than 7.5 kg
Dose	2—3 mg/kg not more than 150 mg (max.)	2—8 mg/kg not more than 600 mg (max.)	2—8 mg/kg not more than 300 mg (max.)
Frequency and administration route	Every 8 weeks subcutaneous	Every 8 weeks subcutaneous	Every 8 weeks subcutaneous
Indication	**HIDS/TRAPS/FMF**	**HIDS/TRAPS/FMF**	**HIDS/TRAPS/FMF**
Registration date	September 23, 2016	March 2, 2017	November 17, 2016
Age / body weight	Children and adults	Children and adults	Children and adults
Dose	≤40 kg: 2 mg/kg >40 kg: 150 mg Up to 300 mg (max.)	≤40 kg: 2 mg/kg >40 kg: 150 mg Up to 300 mg (max.)	≤40 kg: 2 mg/kg >40 kg: 150 mg Up to 300 mg (max.)
Frequency and administration route	Every 4 weeks subcutaneous	Every 4 weeks subcutaneous	Every 4 weeks subcutaneous

Note. FDA: Food and Drug Administration (USA); EMA: European Medicines Agency; FCAS: Familial Cold Autoinflammatory Syndrome; MWS: Muckle-Wells syndrome, cryopyrin-associated autoinflammatory disease; CINCA/NOMID: Chronic Infantile Onset Neurologic Cutaneous Articular/Neonatal Onset Multisystem Inflammatory Disease.

CAPS patients at the age of 8 months and older with a bodyweight of 10 kg at a dose of 1–2 mg/kg per day. A number of open-label non-randomized prospective studies published since 2006 have shown the rapid onset of the effect and the safety of using this drug in CAPS patients [16, 28–32]. It is reported that canakinumab and anakinra can be used not only for CAPS but for other mAIDs as well. In 2013, information was published that said about 30 patients with colchicine-resistant FMF (crFMF) treated with anakinra and 4 patients treated with canakinumab [16]. In 2015, the number of cases described increased from 64 and 40, respectively. A good clinical and laboratory response was noted in all publications. Complete response without disease recurrence and without attacks was reached in 76.5 % of the patients included in the anakinra group and 67.5 % of the patients included in the canakinumab group [16, 33–35]. In addition, it was reported that in patients with AA amyloidosis, a decrease in proteinuria was observed when using both drugs [16]. Patients with TRAPS were reported to have the high efficacy of IL-1 inhibitor and its superiority over etanercept (ETC), which they had received earlier, was noted. CLUSTER, a multicenter randomized controlled study (RCS), evaluated the efficacy and safety of canakinumab when treating the main mAIDs: TRAPS, HIDS, and crFMF. The most important outcome of the study described was that canakinumab, which had been already used in the world, was authorized for these diseases in the Russian Federation in 2016 (See the Table) [14–16].

There is another IL-1 inhibitor, rilonacept, that has not been authorized in Russia but is widely used in other countries along with canakinumab and anakinra for mAIDs treatment [16, 36].

The systematic review covering the GEBD treatment of mAIDs from 2000 to 2017 provides the results analyzed for 72 studies (both multicenter and pilot RCSs) [37]. More than half of the works were published in the last 5 years, 38 of them were carried out in European countries and 9 in the USA. In general, both children (minimum age of 44 days) and adults (maximum age of 80 years) were included in the studies [36–38]. The duration of observational studies was different: from 4 months to 5 years. A partial or complete response to the therapy was considered. Canakinumab and anakinra were prescribed more often as a treatment for CAPS and HIDS/MKD, whereas the combination of ETC with canakinumab and anakinra were prescribed for TRAPS [37, 39]. The poor response was obtained when treating the CAPS (CINCA/NOMID) patients with the combination of ETC [37], and there is conflicting information on the efficacy of tocilizumab (TCZ) in some of such patients [16, 37]. In HIDS/MKD, preference was given to short-acting IL-1 inhibitor (anakinra), although, according to the data obtained during RCS, canakinumab was also highly effective [14, 37, 40]. J. Kuemmerle-Deschner et al. [37] complete response to canakinumab was reported in all patients during a 5-year observation. When evaluating the treatment safety, the conducted studies demonstrated good tolerability of canakinumab, at the same time, some patients developed local skin reactions in response to anakinra and ETC administration.

A number of studies have been devoted to drug displacement between IL-1 inhibitors, mainly in CAPS (11) and HEADS/MOD (3), from anakinra to canakinumab (9) and vice versa (3) [37, 41, 42]. The most common reasons for the anakinra replacement with canakinumab were insufficient efficacy, difficulties related to frequent daily injections, injection-site reactions, as well as personal preferences of patients. The reasons why the repeated drug displacement took place (from canakinumab to anakinra) mostly were an inadequate response to treatment, the development of adverse events, as well as pregnancy, in which anakinra intake as a short-acting drug is more preferable [37, 43]. There is not much data on TCZ, infliximab (IFX), and adalimumab (ADA) in mAIDs since these drugs are not widely used in

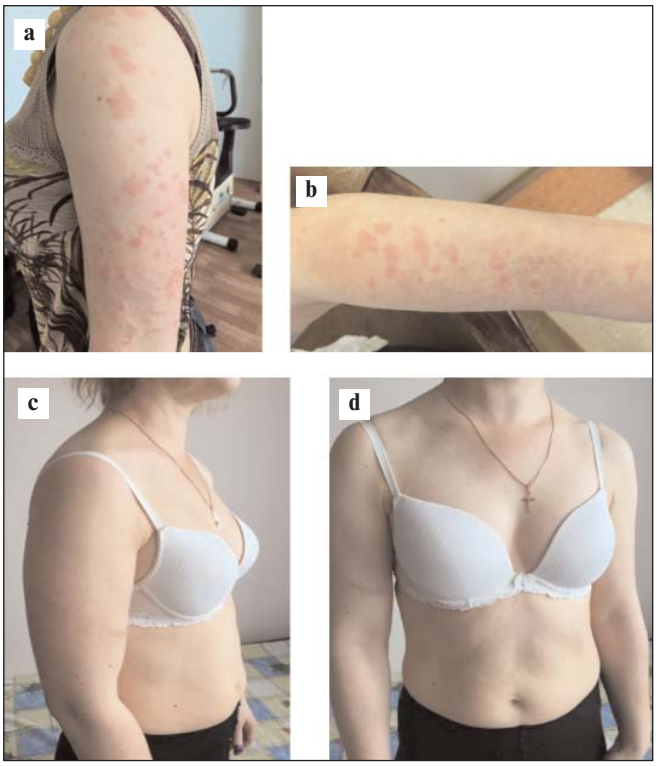

Fig. 1. *Cutaneous manifestations of MWS in patient S. before (a, b) and during (c, d) iIL1 therapy*

Fig. 2. *Ophthalmic manifestations of MWS in patient S. before (a) and during (b) iIL1 therapy*

these conditions and are not approved for use. TCZ efficacy has been reported in isolated FMF, TRAPS, and HIDS/MKD patients with the ineffectiveness of IL-1 inhibitors and other drugs [16]. According to some data, in 64–75 % of patients with amyloidosis associated with FMF, TCZ therapy successfully controlled the disease activity and decreased proteinuria. However, after therapy had been discontinued, proteinuria would occur and disappear again if the therapy continued. IL-6 inhibitor therapy has proved to be effective in some TRAPS and HIDS patients who are resistant to IL-1 inhibitor and TNF α inhibitors (iTNFα), unlike in CAPS patients, for whom a negative result has been obtained [16]. ITNFα (ETC, ADA, IFX) was used successfully to treat FMF, especially when it was followed by chronic articular manifestations, which allowed to include those inhibitors into modern recommendations on FMF patient management [8, 15, 16, 44–46]. According to the Eurofever Registry, a complete or partial response to ETC therapy has been obtained in 7 of 9 patients, to IFX a complete response has been obtained in 7 patients, and in 8 patients a partial response has been reported, 3 patients had a complete response to ADA therapy, 2 patients had a partial response to it; when administrating ETC (n=121), better results have been obtained in TRAPS patients: in 88 %, effectiveness was satisfactory, along with that a complete response has been reported in 26 % of the patients, while attacks either did not occur or their intensity decreased, but secondary ineffectiveness occurred over time [12, 13, 16]. The use of other iTNFα (IFX and ADA) for TRAPS treatment was associated with reverse reactions, absence of any effect, or deterioration [12, 13].

Case report

Female patient S.*, 43 y.o., sought medical advice in the V.A. Nasonova Research Institute of Rheumatology in May 2015 for the first time. Medical history: suffers from the condition since birth. The disease onset was followed by cutaneous maculopapular rash and urticaria-like skin lesions, which later were persistent almost all the time, the temperature rising to 38.0° C with chills. At the age of 5 years, there was pain and swelling in one of the knee joints with limited movement in it. The symptoms resolved within 1 week. Subsequently, recurrent pain and swelling in both wrist, elbow, and knee joints, small joints of the hands, and feet occurred regularly, which became weekly from the age of 13 years. At the age of 5–6 years, redness of the eyes appeared with a sharp increase in symptoms starting from the age of 13 years. Almost at the same time (from the age of 6 years), a recurrent aphthous stomatitis, recurrent abdominal pain (from the age of 6–7 years) appeared. In primary school age, there was an increase in cervical lymph nodes. Leukocytosis up to 27$\cdot$10^9/L has been observed in blood samples since the age of 17 years. The patient was examined by a hematologist (a sternal puncture was performed, hematooncological pathology was excluded). Since she was 21 y.o., the patient has suffered from conjunctivitis. At first, its symptoms occurred once in two weeks, but since she was 40 y.o., these symptoms have appeared persistently. Since 36 y.o., the patient has suffered from daily pain in the umbilical region. A persistent increase in acute phase reactants: ESR up to 35 mm/h, CRP up to 18 mg/L. At the age of 39 years, genitalia aphthae episode was observed. The patient constantly has the following complaints: lethargy, fatigue, lack of energy, impaired productivity. In 2015, when examined at Federal State Budgetary Institution "Helmholtz National Medical Research Center for Eye Disorders and Diseases" of the Ministry of Health of Russia, the patient was diagnosed with stromal corneal dystrophy. In the same year, based on the audiogram results, Degree II sensorineural hearing loss was observed. The pThr350Met gene mutation (c.1049C>T) was determined during molecular genetic study of the NLRP3 gene (CIAS1). During the follow-up, symptomatic treatment (NSAIDs, antihistamines and aminoquinoline drugs) was administered, which proved to be inefficient. Comorbidities: duodenal ulcer, chronic pancreatitis, and tonsillitis, Degree II diffuse goiter.*

Based on medical history, complaints, examination data, the following diagnosis has been established: cryopyrin-associated periodic syndrome: Muckle–Wells syndrome (MWS). Since October 2015, the patient has been prescribed canakinumab therapy at a dose of 150 mg subcutaneously once every 8 weeks. A complete response to therapy was received: there was an improvement in the general condition, relief of non-specific constitutional symptoms, rash, other systemic inflammatory and organ manifestations of the disease (Fig. 1), normalization of acute phase reactants, restoration of performance capability. A significant improvement has been reported in ocular manifestations (Fig. 2), conjunctivitis did not recur, however, complete restoration of eye structures (corneal dystrophy) and hearing according to the audiogram has not been achieved. The patient tolerated the therapy satisfactory.

Family health history: MWS has been confirmed for the patient's 14-year-old son. He has been taking canakinumab since 2015, the complete response to therapy was noted.

Discussion. This clinical case demonstrates a belated diagnosis (43 years after the onset of the symptoms) in CAPS (MWS) patient and a pronounced positive response to the IL-1 inhibitor therapy, which, if prescribed timely, could have prevented serious and intractable organ damage.

MAIDs include disorders that are characterized by repeated episodes of a sudden noninfectious inflammation of a known genetic nature. Most of the mAIDs have a severe course and a serious prognosis, which depends on timely diagnosis and early initiation of therapy. Treatment of such patients is associated with many difficulties. GEBD therapy for mAIDs has been used in clinical practice for a long period of time and become a necessary part of rheumatic diseases (RD) treatment. However, the predominant use of iTNFα, IL-6 inhibitor, and other GEBDs in RD in pediatric patients did not allow to fully evaluate the effectiveness of IL-1 inhibitors, which today have become a targeted therapy of mAIDs. The successful introduction of IL-1 inhibitors in periodic fever syndromes has expanded their use in other diseases of an autoinflammatory nature, i.e. in systemic juvenile arthritis (sJA), adult Still's disease (ASD). The effect of canakinumab, observed already in the first days after the initiation of therapy and persisting in the future, can be evaluated as excellent in terms of controlling systemic manifestations in all patients, regardless of age. Treatment outcome has once again proven the key role of IL-1β in the pathogenesis of the most common mAIDs.

The experience of using GEBDs in mAIDs patients, limited mainly by IL-1 inhibitors, has demonstrated a pronounced response to therapy, primarily in pediatric patients and adults with different CAPS phenotypes. There is brief experience due to the rarity of the pathology and the relatively recent appearance of IL-1 inhibitors in Russia.

Despite the success that was reached in the last few years of mAIDs treatment, there are some questions that still should be answered [20]:

- How often do mAIDs patients require GEBD treatment?
- What is a "portrait" of a patient who should be prescribed GEBD?
- How can we determine the resistance to any of the GEBDs in mAIDs patients or an inadequate response to it?
- What is the "therapeutic window" to initiate the GEBD treatment?
- Which GEBD should we use first?
- When should we replace one GEBD with another one and which exactly should we choose?
- How can we demonstrate GEBD effect on secondary amyloidosis prevention?
- What kind of tactics should we choose for GEBD treatment of pregnant and breastfeeding patients?
- How to increase the intervals between drug injections and is it even possible to stop any treatment with the development of remission?
- How can we determine the right moment to initiate an on-demand therapy after a prolonged continuous GEBD administration?

Conclusion. These questions are still debatable. The use of Janus kinase inhibitors seems to be one of the promising areas of mAIDs treatment, for example, in patients with crFMF with resistance to IL-1, IL-6, and iTNFα.

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