ORIGINAL INVESTIGATIONS

Biological disease-modifying antirheumatic drugs in the main monogenic autoinflammatory diseases treatment. Experience of application in rheumatological practice

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Objective: *to assess the frequency of prescription, efficacy and tolerability of biological disease-modifying antirheumatic drugs (bDMARDs) therapy in patients with major monogenic autoinflammatory diseases (mAID) according to the Federal Rheumatology Center clinical practice.*
Patients and methods. *From 2008 to 2020 years, 158 patients with mAID were included in the study, 53 of whom were prescribed bDMARDs: 12 patients had Familial Mediterranean Fever (FMF); 26 – Cryopyrin-Associated Periodic Syndromes (CAPS), including 21 patients with Muckle-Wells Syndrome (MWS) and 5 – with Chronic Infantile Onset Neurologic Cutaneous Articular / Neonatal Onset Multisystem Inflammatory Disease (CINCA/NOMID), 12 patients had Tumor necrosis factor (TNF) receptor-Associated Periodic Fever Syndrome (TRAPS) and 3 – Hyper-Immunoglobulinemia D-syndrome (HIDS/MKD). Among all these patients 25 were male and 28 female, aged 1.5 to 44 years, 45 were children (under 18) and 8 adults. Interleukin 1 inhibitors (iIL1) were prescribed in accordance with the following scheme: canakinumab – subcutaneously 2–5 mg/kg or 150 mg per injection, every 4–8 weeks; anakinra – subcutaneously 1–5 mg/kg or 100 mg/day, daily. Etanercept (ETC) was injected subcutaneously 0.4–0.8 mg/kg 1–2 times a week, and adalimumab (ADA) was injected subcutaneously 20–40 mg once every 2 weeks. Tocilizumab (TCZ) was administered intravenously, 8–12 mg/kg once every 2–4 weeks. The duration of the disease at the time of treatment initiation ranged from 1 to 44 years. The duration of bDMARDs therapy in patients with mAID ranged from 1 month to 12 years.*
Results and discussion. *From 158 patients with mAID, in 53 (33.5%) bDMARDs were administered. They were used more often in patients with CAPS (56.6%), and less often – in TRAPS (26.4%), FMF (28.3%) and HIDS/MKD (5.7%). iIL1 were the most frequently prescribed bDMARDs (90.6%): canakinumab (in 38 patients) and anakinra (in 10), they were mainly used in patients with CAPS, in 2/3 of patients with TRAPS, HIDS/MKD and colchicine-resistant FMF. During the first days of iIL1 treatment, all patients with mAID showed a statistically significant clinical improvement: normalization of general condition, emotional recovery, relief of fever, disappearance of rash, decrease in the severity of lymphadenopathy and hepatosplenomegaly, relief or significant positive dynamics of eye symptoms, subjective improvement in hearing and audiogram (with dynamic control in patients with CAPS), decrease in the level of acute phase markers (in all cases). In 7 patients with CAPS, who received anakinra, after a positive response was achieved, switching to canakinumab was performed, which maintained the full effectiveness of therapy. TCZ (in 7 patients) and inhibitors of tumor necrosis factor α (iTNFα) – ADA (in 3) and ETC (in 4), – were used less frequently. iTNFα were more often prescribed to FMF patients with a complete response to treatment. Tolerability of bDMARD therapy was satisfactory in all patients.*
Conclusion. *Currently, iIL1 are the first line of therapy among biological agents for mAID, especially in patients with CAPS. If they are ineffective or intolerant in certain situations, alternative bDMARDs (iTNFα and IL6 inhibitors) can also be used, but this issue needs further study.*

Key words: *autoinflammatory diseases; FMF; CAPS; TRAPS; HIDS/MKD; biological therapy; Interleukin 1 inhibitors.*
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Systemic autoinflammatory diseases (SAIDs) are caused by systemic aseptic inflammation associated with the activation of the innate immune system. A genetic defect triggers accelerated (inadequate to the actual needs of the macroorganism protection) development of a supramolecular protein complex known as inflammasome, leading to excessive production of interleukin (IL) 1β [1, 2]. IL-1β is a member of the proinflammatory cytokine family and plays a key role in the development of systemic inflammatory response [3, 4]. These underlying pathogenetic mechanisms and clinical and laboratory manifestations are mainly typical for certain conditions from a large group of monogenic AIDs (mAIDs), such as inflammasome-mediated diseases, which include Familial Mediterranean Fever (FMF), cryopyrin-associated periodic syndromes (CAPS), Tumor necrosis factor Receptor-Associated Periodic Fever Syndrome (TRAPS), and Hyper-Immunoglobulinemia D-syndrome (HIDS/ MKD).

The mAIDs treatment approaches have undergone significant changes over the last decade. A breakthrough advance in the therapy of these patients became the use of genetically engineered biological drugs (GEBD), in particular IL-1 receptor antagonists (IL-1RA) or IL-1 inhibitors that was driven by the underlying pathogenetic mechanisms of the diseases, the development of which stems from the excessive production of one of the most potent proinflammatory cytokines, i.e. IL-1β [5C16].

Despite the globally accumulated experience in AIDs therapy, many of its aspects, especially the use of GEBD, are not standardized, and require further research. In the FSBSI «V.A. Nasonova Research Institute of Rheumatology», patients with mAIDs are also treated with GEBDs (CAPS, TRAPS, FMF, HIDS).

The **objective** of the study was to assess the frequency of prescription, efficacy, and tolerability of GEBD therapy in patients with major mAIDs based on data from the Federal Rheumatology Center.

Table 1. Characteristics of patients with mAID, who received bDMARDs

Parameter	FMF	CAPS	Diagnosis TRAPS	HIDS/MKD	Total
Patients, n (%)	12 (22.6)	26 (49.1)	12 (22.6)	3 (5.7)	53 (33.5)
Sex, males/females, n (%)	7/5	12/14	6/6	0/3	25/28
Age, years	4.5 to 38	1.5 to 44	4.5 to 21	4 to 17	-
Duration of disease	1 mo to 15.5 yrs	1.5 to 44 yrs	3 mos to 21 yrs	3.5 to 15.5 yrs	-
ETA*, n (%)	3 (25.0)	-	1 (8.3)	-	4 (7.5)
ADA*, n (%)	2 (16.7)	-	1 (8.3)	-	3 (5.7)
TCZ*, n (%)	1 (8.3)	2 (7.7)	3 (25.0)	1 (33.3)	7 (13.2)
Canakinumab, n (%)	8 (66.7)	20 (76.9)	9 (75.0)	1 (33.3)	38 (71.7)
Anakinra#, n (%)	1 (8.3)	8 (30.8)	-	1 (33.3)	10 (18.9)

* Indications for FMF, CAPS, TRAPS, HIDS/MKD are not registered in the Russian Federation. # In the Russian Federation, only indication for CAPS is registered.

Patients and methods. From 2008 to 2020, a total of 158 patients with mAIDs were enrolled in the study, with 53 subjects receiving GEBDs, including 12 subjects with FMF, 26 with CAPS (21 with MWS and 5 with CINCA/NOMID), 12 with TRAPS, and 3 with HIDS. Patient characteristics are shown in Table 1. There were 25 male and 28 female subjects aged 1.5 to 44 years of age, with 45 children (up to 18 years of age) and 8 adults. The IL-1RA treatment regimen used was as follows: canakinumab administered subcutaneously at a dose of 2 to 5 mg/kg, or 150 mg per injection, every 4 or 8 weeks, and anakinra 1 to 5 mg/kg, or 100 mg/day, subcutaneously, once daily. Etanercept (ETC) was administered subcutaneously at a dose of 0.4 to 0.8 mg/kg once or twice a week, adalimumab (ADA) 20 to 40 mg subcutaneously QOW. Tocilizumab (TCZ) was given intravenously at a dose of 8 to 12 mg/kg once every 24 weeks. The duration of the disease at the time of treatment start ranged from 1 to 44 years. The duration of therapy with GEBDs in patients with mAIDs ranged from 1 month to 12 years.

Results. Fifty-three (33.5%) of 158 patients with mAIDs received treatment with GEBDs. Before their prescription, the majority of patients had inflammatory manifestations (Table 2), where fever, skin rashes, and articular symptoms (arthralgia or osteoarthritis in 79.2%) prevailed. Ocular involvement was seen in almost half of the patients represented by conjunctivitis and/or uveitis, keratopathy (mainly in CAPS and TRAPS, with 76.9 and 33.3% of patients, respectively).

Gastrointestinal symptoms (abdominal pain, nausea, vomiting) were present in half of the patients, mainly with FMF and TRAPS. Hearing impairment in the form of sensorineural hearing loss was not so common (20.8%) (in 38.5% of CAPS patients). There were also more rare symptoms, such as oral aphthous elements, lymphadenopathy, manifestations of the central nervous system or cardiorespiratory (CR) system manifestations, and other organ diseases.

Before the initiation of therapy with GEBDs, most patients received symptomatic treatment or conventional antirheumatic therapy (Table 3). Half of the patients needed the use of glucocorticoids, GCs (most often patients with CAPS and TRAPS), about one-third of subjects took colchicine (almost all FMF

Table 2. Clinical manifestations in patients with mAID before bDMARDs administration, n (%)

Sign	Diagnosis				
	FMF (n = 12)	CAPS (n = 26)	TRAPS (n = 12)	HIDS (n = 3)	Total (n = 53)
Fever	12 (100)	25 (96.2)	12 (100)	3 (100)	52 (98.1)
Skin lesion	8 (66.7)	26 (100)	11 (91.7)	1 (33.3)	46 (86.8)
Stomatitis	4 (33.3)	9 (34.6)	1 (8.3)	1 (33.3)	15 (28.3)
Genital aphthous ulcers	0	3 (11.5)	0	0	3 (5.7)
GI tract involvement	11 (91.7)	6 (23.1)	10 (83.3)	1 (33.3)	28 (52.8)
CP involvement	7 (58.3)	1 (3.8)	3 (25)	0	11 (20.8)
CNS involvement	1 (8.3)	8 (30.8)	4 (33.3)	1 (33.3)	14 (26.4)
Osteorthritis / arthralgias	11 (91.7)	20 (76.9)	10 (83.3)	1 (33.3)	42 (79.2)
Lymphadenopathy	0	10 (38.5)	5 (41.7)	2 (66.7)	17 (32.1)
Eye involvement	1 (8.3)	20 (76.9)	4 (33.3)	0	25 (47.2)
Hearing impairment	0	10 (38.5)	1 (8.3)	0	11 (20.8)

Note. GI tract = gastrointestinal tract

Table 3. Therapy of patients with mAID before bDMARDs administration, n (%)

Biologic	Diagnosis				
	FMF (n = 12)	CAPS (n = 26)	TRAPS (n = 12)	HIDS (n = 3)	Total (n = 53)
GC	4 (33.3)	13 (50)	9 (75)	-	26 (49.1)
MTX	3 (25)	5 (19.2)	3 (25)	1 (33.3)	12 (22.6)
Hydroxychloroquine	-	2 (7.7)	1 (8.3)	-	3 (5.7)
Cyclosporine	1 (8.3)	1 (3.8)	1 (8.3)	1 (33.3)	4 (7.5)
Colchicine*	12 (100)	1 (3.8)	3 (25)	-	16 (30.2)
Cyclophosphan	-	-	1 (8.3)	-	1 (1.9)
Sulfasalazine	1 (8.3)	-	-	-	1 (1.9)

*Only indication for FMF is registered in the Russian Federation.

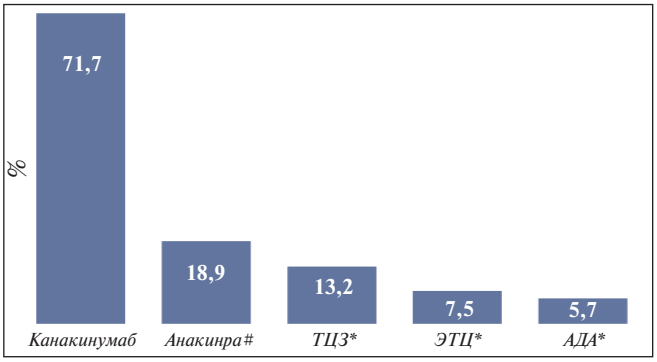

Fig. 1. *Frequency of use of various bDMARDs in patients with mAID. Here and in Fig. 2: # – only indication for CAPS is registered in the Russian Federation; * – indications for FMF, CAPS, TRAPS, HIDS/MKD are not registered in the Russian Federation*

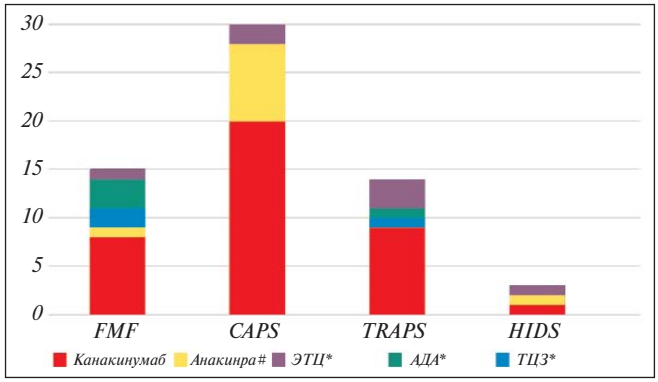

Fig. 2. *Spectrum and frequency of bDMARDs usage in patients with major mAID*

patients). Disease-modifying anti-rheumatic drugs (DMARDs) were administered in 69.8% of patients, including methotrexate (MTX) in 22.6%, and less often other antirheumatic drugs (hydroxychloroquine, cyclosporine A, azathioprine, cyclophosphamide, sulfasalazine). If these drugs were shown to lack or have no efficacy, biological therapy was prescribed.

Among biologics, IL-1RAs were most frequently used (90.6%), including canakinumab (in 38 patients) and anakinra (in 10 subjects). The majority of CAPS patients, two-thirds of TRAPS or colchicine-resistant FMF patients received these two drugs (Table 1, Fig. 1, Fig. 2). After achieving clinical response, seven CAPS patients previously treated with anakinra were switched to canakinumab, with overall clinical efficacy appeared to be preserved.

Less commonly were used TCZ, ie in 7 (13.2%) patients, and tumor necrosis factor-alpha inhibitors (TNFα inhibitors), including ADA in 3 (5.7%) and ETC in 4 (7.5%), which in most cases were prescribed for FMF.

With IL-1RA treatment, all patients with mAIDs demonstrated significant clinical improvement just over the first few days, including the normalization of well-being, emotional recovery, relief of fever, skin rash resolution (Fig. 3), a decrease in the severity of lymphadenopathy and hepatosplenomegaly, relief or significant beneficial changes in eye symptoms (Fig. 4), subjective improvements in hearing and audiogram recordings (with follow-up in CAPS patients), and decreased levels of acute-phase reactants in all subjects.

In a severe CINCA/NOMID patient (the duration of disease at the time of diagnosis was 17 years, there was a significant delay in growth, physical and mental development), 5-year therapy resulted in complete relief of inflammatory manifestations, body height gain by 14 cm, the appearance and development of absent secondary sexual characteristics, and improvement of cognitive functions and social adaptation.

In all patients, GCs were discontinued, leading to the disappearance of signs of Cushing's syndrome induced by treatment. The therapeutic effect persisted in all patients. The exceptions were a female patient with TRAPS (missed the next injection of the drug) and the above-mentioned patient with severe CAPS (CINCA/NOMID), who subsequently had a relapse of their disease. In a patient with severe CAPS, the interval between injections of canakinumab was cut from 8 to 4 weeks. In both patients, there was complete recovery of treatment efficacy.

The therapy was generally well-tolerated. Adverse events (AEs) were reported in 2 patients with mAIDs. The young female patient with MWS developed recurrent skin lesions represented by granuloma annulare, which, following a detailed examination with all other potential etiologies ruled out, were regarded as a fungal infection. With antifungal therapy, an improvement was demonstrated, and the suspended canakinumab treatment was resumed. After the first three injections of canakinumab, a TRAPS patient had recurrent furunculosis, which was regarded as a treatment-emergent AE. The conventional treatment of furunculosis was instituted, with no further relapses.

In an MWS patient, after 1.5 years of treatment, GEBD was discontinued in view of a contact with a TB patient with a positive DST, and TB preventive therapy was prescribed, followed by

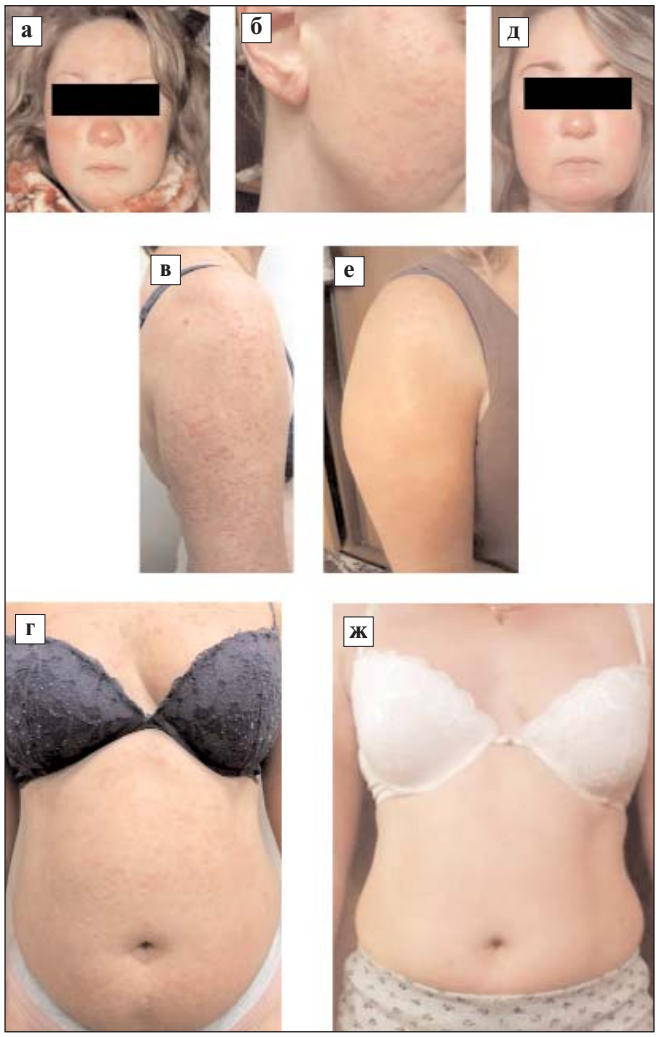

Fig. 3. *Skin rashes in a patient with CAPS before (а–г) and during iIL1 therapy (д–ж)*

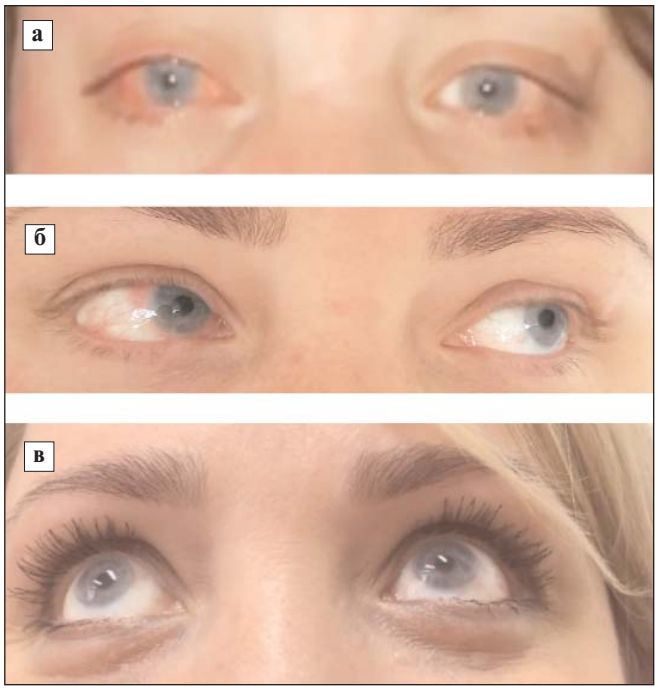

Fig. 4. *Ocular manifestations (conjunctivitis) in a patient with CAPS before (а, б) and during iIL1 therapy (в)*

reinitiation of IL-1RA treatment. No other AEs were reported. All the remaining patients continue receiving canakinumab to date. The maximum duration of treatment was 12 years.

We also followed up patients who had COVID-19; they had a mild infection in the setting of therapy with IL-1RAs, there was no need to suspend or change the biologic regimen.

TNFα inhibitors were much less frequently prescribed to patients with AID (5.7 to 7.5% cases), mainly for FMF associated with chronic arthritis, which is consistent with literature data [6, 8, 9], while TCZ (13.2%) was used for CAPS and TRAPS, with good efficacy observed in all cases (Table 1). The GEBD tolerability was also satisfactory in all patients, there was no AEs and serious adverse events (SAEs) reported. However, it is still premature to draw any conclusions about the efficacy and tolerability of TNFα inhibitors and IL-6 inhibitors in mAIDs due to the small sample of patients and the lack of data from randomized clinical trials.

Discussion. High inflammatory status in AIDs, the presence of manifestations from different organs and systems, as well as serious complications, such as amyloidosis and other organ diseases, are regarded as a ground for the initiation of active anti-inflammatory therapy.

The emergence of GEBDs in recent decades led to great advances in the treatment of AIDs, allowing them to modify the course of the disease, improve the prognosis and quality of life of patients. In our study, IL-1RAs were predominant options, which were successfully used in the vast majority of patients with mAIDs. Especially high efficacy of such therapy was seen in CAPS and TRAPS, which is consistent with the data presented by A. Soriano et al. [12] and J.B. Kuemmerle-Deschner et al. [13]. The pooled domestic experience of using IL-1RAs, first of all, canakinumab, in patients with mAIDs indicates its good efficacy and tolerability. Evidence on the use of biological therapy for FMF, HIDS, and TRAPS is limited, however, the high efficacy and safety of IL-1RAs is also apparent in this population. Our experience of using IL-1RAs for FMF and HIDS/MKD is not as extensive as that of for CAPS, as an example. On one hand, this indicates the lesser need for their use for FMF, since in the majority of these patients, the most effective drug is colchicine. On the other hand, the occasional occurrence of HIDS/MKD in the clinical practice of a rheumatologist and the relatively favorable prognosis of this disease preclude from assessing the actual efficacy of IL-1RAs. However, there are a series of Russian-based observations demonstrating their very successful use in this population of patients [17].

While monitoring treatment with IL-1RAs, we revealed no SAEs and reported AEs did not lead to the complete discontinuation of the drugs.

At present, the experience of using other GEBDs (TNFα or IL-6 inhibitors) in patients with recurrent febrile syndromes is still limited and further research is needed. In our cohort, TNFα or IL-6 inhibitors were given to approximately 10% of patients who were initially treated for systemic juvenile arthritis using the conventional regimens, and only during follow-up, after detection of a mutation in the corresponding genes, their diagnosis was changed. However, due to the clinical response, the treatment regimen in these patients was not modified. We believe these drugs may be used as salvage therapy. We did not prescribe ETC for TRAPS, because there is an alternative drug, canakinumab, approved for this condition.

Our findings based on real-world practice demonstrate that pathogenetic therapy was prescribed to only one-third of patients with mAIDs, which reflects a personalized approach to their management. There is a need for therapy in such patients due to the disease severity and the development of complications, often associated with the mutation type and penetrance. For most patients with mAIDs, therapy, in particular with IL-1RAs, is absolutely essential and lifelong. The issue of providing patients with these highly effective, but expensive drugs after initiation of therapy in the federal center of tertiary care requires more close attention from the authorities.

Conclusion. Therefore, based on a number of previous studies and the experience of treating our cohort of patients, it can be concluded that IL-1RAs are at present the first-line GEBDs for mAIDs.

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Conflict of Interest Statement

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