ORIGINAL INVESTIGATIONS

Analysis of clinical manifestations and spectrum of pharmacotherapy in Moscow and St. Petersburg cohorts of patients with adult-onset Still's disease

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Adult-onset Still's disease (AOSD) is a systemic autoinflammatory disease of unknown etiology characterized by clinical manifestations such as fever, non-stable maculopapular rash, arthritis and/or arthralgias and leukocytosis with neutrophilia.

Objective: *to analyze the spectrum of clinical manifestations of AOSD and pharmacotherapy in real clinical practice.*

Material and methods. *A cross-sectional study included 111 patients with a confirmed diagnosis of AOSD according to the Yamaguchi criteria, who were treated in two large Russian centers from 2019 to 2022: V.A. Nasonova Research Institute of Rheumatology (Moscow) and Almazov National Medical Research Centre (Saint Petersburg).*

Results and discussion. *We analyzed the spectrum of clinical manifestations throughout the course of the disease. The spectrum of clinical manifestations of AOSD in our study was shown to be similar to the results of other studies. It was found that the frequency of the different clinical manifestations did not differ significantly.*

The majority of patients (74%) in our cohort received glucocorticosteroids (GC) in combination with disease-modifying antirheumatic drugs (DMARDs) or biologic DMARDs (bDMARDs). Monotherapy with GC was used in only 9% of patients. Up to 80% of patients received methotrexate (MTX) at various stages of the disease. For the treatment of patients refractory to GC and MTX therapy, bDMARDs were prescribed (44% of cases), most frequently interleukin-6 inhibitors (34%). In the St. Petersburg cohort, 13 (31.7%) of 41 patients were taking colchicine, which enabled control of disease manifestations and a reduction in the need for GC in 9 of them.

Conclusion. *Thus, we can draw a preliminary conclusion about the presence of steroid dependence in patients with AOSD. Up to 79.3% of AOSD patients are forced to take GC for a long period of time, which is associated with the risk of complications. Further studies on the optimal profile of bDMARDs are needed, as well as the role of colchicine as a potential therapeutic option for certain clinical and immunological subtypes of AOSD.*

Keywords: *adult-onset Still's disease; symptoms; diagnosis; treatment.*
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Adult-onset Still's disease (AOSD) is a systemic autoinflammatory disease of unknown etiology, characterized by clinical manifestations such as fever, unstable maculopapular rash, arthritis and/or arthralgias and leukocytosis with neutrophilia. These symptoms usually occur in combination with pharyngitis, polyserositis, lymphadenopathy and hepatosplenomegaly. None of the clinical and laboratory signs are highly specific for AOSD, which complicates the diagnosis and requires a differential diagnosis to exclude other rheumatic diseases as well as hematological (leukemia, lymphomas) and infectious (sepsis, infective endocarditis) diseases.

Recently, the distinction of AOSD as its own nosology has been disputed and it is interpreted in a continuum of a single nosological form with systemic variant of juvenile idiopathic arthritis (JIA). AOSD is named after the English pediatrician George Still, who in 1897 described a group of children with symptoms that are now classified as JIA [1]. Later, in 1971, Eric Bywaters published an observation of 14 adult patients who also showed clinical symptoms previously described in children (skin rash, fever, polyarthritis, etc.), and AOSD was isolated as a distinct disease [2]. However, further comparative analysis of molecular biological data (expression profiles) and genetic studies led us back to the assumption that JIA and AOSD are clinical variants of a single nosological form [3].

AOSD belongs to the group of orphan diseases, the incidence varies between 0.16 and 0.4 cases per 100,000 of population. In the world literature, epidemiological data are incomplete and do not allow comparison of the prevalence and incidence of AOSD in different populations. All information on rare diseases comes from a few observational studies, descriptions of patient cohorts and case series. As a result, there is a lack of convincing data on prognostic factors, characteristics of the long-term course, atypical clinical manifestations and other aspects of AOSD.

The diagnosis of AOSD is complicated by the lack of pathognomonic clinical, laboratory or pathological signs. Several variants of diagnostic criteria have been proposed, but M. Yamaguchi's classificational criteria are the most commonly used in clinical practice [4].

Due to the small number of studies, optimal approaches to the treatment of AOSD have not yet been developed. Currently, there are no international clinical guidelines for the treatment of AOSD recognized by EULAR (European Alliance of Associations for Rheumatology) and ACR (American College of Rheumatology).

Table 1. Demographic characteristics of the patients

Parameter	Almazov Research Center cohort (n=41)	NIIR cohort (n=70)
Women, n (%)	30 (73)	49 (70)
Men, n (%)	11 (27)	21 (30)
Age at the onset of the disease, years, Me [25-й; 75-й percentile]	27,5 [23,1; 32]	32 [24; 42]
Age at the time of the study, years, Me [25-й; 75-й percentile]	35,8 [30,5; 40,7]	37 [27; 44]

Table 2. Clinical and laboratory manifestations of AOSD throughout the course of the disease, n (%)

Parameter	Almazov Research Center cohort (n=41)	NIIR cohort (n=70)	Total
Symptoms:			
Fever	41(100)	70 (100)	111 (100)
Arthralgias	37 (90,1)	62 (88)	99 (89.2)
Arthritis	33(80,5)	44 (63)	77 (69.4)
Rash	31 (75,6)	52 (74)	83 (74.8)
Sore throat	20 (48,8)	47 (67)	67 (60.4)
Hepato/Splenomegaly	20 (48,8)	37 (52)	57 (51,3)
Pericarditis	16 (39,0)	22 (31,4)	38 (34,2)
Pleurisy	12 (29,3)	11 (16)	23 (20,6)
Myalgias	20 (48,8)	39 (55,7)	59 (53,1)
Lymphadenopathy	21 (51,22)	32 (45,7)	53 (47,7)
Course of the disease:			
Chronic	23 (56)	16 (23)	39 (35)
Polycyclic	14 (34,2)	53 (76)	67 (60,4)
Monocyclic	4 (9,8)	1 (1)	5 (4,5)
Laboratory features:			
Hyperferritinemia	41 (100)	39 из 57 (68)*	80 (81,6)
ALT, AST elevation before treatment	9 (21,9)	32 (45,7)	42 (36,8)
Leukocytosis before the treatment	41 (100)	51 (73)	92 (82,9)
ANF positivity	1	2	3 (2.7)

Note. AST – aspartate aminotransferase; ALT – alanine aminotransferase; ANF – antinuclear factor. *As a rule, patients with a diagnosed disease are referred to federal institutions. In the Moscow cohort, the majority of patients had been receiving glucocorticoids (GCs) for a long time at the time of referral. Ferritin was not monitored at the place of residence during the clinical activity of the disease, or the results were lost. Thus, only 57 (81%) patients had data on ferritin levels, and only 39 (68%) of them showed an increase.

Since there are no population data on AOSD in our country, no descriptions of patient cohorts or information on the spectrum of clinical and laboratory manifestations, we attempted to analyze the combined cohort of patients with AOSD observed in federal centers of the Russian Federation.

Objective. To evaluate the spectrum of clinical manifestations of AOSD and the type of pharmacotherapy used in this disease in real-life clinical practice.

Material and methods. The cross-sectional study included patients with a confirmed diagnosis of AOSD at different stages of the disease who were observed in two federal centers: V.A. Nasonova Research Institute of Rheumatology (NIIR, Moscow) and V.A. Almazov National Medical Research Center (St. Petersburg) in 2019–2022. The cohorts were formed from patients who were hospitalized in these institutions. To select those patients, we conducted a search in the local information systems for a diagnosis of M06.1 "adult-onset Still's disease". Medical documentation from the period of hospitalization and in some cases from the period of outpatient observation was analyzed.

Inclusion criteria: Diagnosis of AOSD according to the criteria of M. Yamaguchi 1992.

Exclusion criteria: Presence of a concomitant disease whose clinical and/or laboratory manifestations were consistent with AOSD and would complicate the differential diagnosis.

Statistical data processing was performed using MS Excel. Descriptive statistics are presented as median and interquartile range (Me [25th; 75th percentile]).

Results. The cohorts included 70 patients from NIIR, and 41 patients from V.A. Almazov National Medical Research Center. Most patients were female, the median age at the time of hospitalization was 32.3 [27; 38] years. The demographic characteristics of the two patient cohorts were comparable (Table 1)

AOSD is a highly heterogeneous disease. Furthermore, the severity and spectrum of clinical manifestations within individual episodes of AOSD can change over the course of the disease, which is why the cumulative occurrence of the symptom was analyzed over the entire disease period (Table 2).

Most patients were receiving combination therapy at the time of enrolment in the study (Table 3).

In our research, up to 80% of patients in the Moscow cohort received MTX at various stages of the disease, but only in 8 cases it was possible to reduce the dose of GCs and discontinue them completely without exacerbation. 44% of patients received biologic disease-modifying antirheumatic drugs (bDMARDs), most frequently interleukin 6 inhibitors (iIL6) – 34%. When analyzing the spectrum of bDMARDs used during the disease in the Moscow

Table 3. Spectrum of pharmacotherapy in patients with AOSD, n (%)

Parameter	Almazov Research Center cohort (n=41)	NIIR cohort (n=70)	Total
GC (in combination)	19 (46)	63 (90)	82 (73,9)
MTX (in combination)	16 (39)	57 (81)	73 (65,8)
GC + MTX	13 (31,6)	56 (80)	69 (62,2)
MTX (monotherapy)	5 (12,2)	8 (11)*	13 (11,6)
GC (monotherapy)	2 (4,88)	5/68 (7)	10/109 (9,2)
Colchicine (total)	13 (31,6)	2 (2,8)	15 (13,4)
bDMARDs (total)	19 (46)	30 (43)	49 (44)
iIL6	17 (41,5)	17 (24)	34 (30,5)
iTNFα	0	8 (11)	8 (7,21)
Anti-B-cell thehrapy	1 (2,44)	1 (1,4)	2 (1,8)
iIL1	1 (2,44)	1 (1,4)	2 (1,8)
iJAK	1 (2,44)	3 (4,3)	4 (3,6)
Drug-free remission	3 (7,2)	1 (1,4)	4 (3,6)

Note. MTX – methotrexate; bDMARDs – biologic disease-modifying antirheumatic drugs; iIL6 – interleukin 6 inhibitors; iTNFα – tumor necrosis factor α inhibitors; iIL1 – interleukin 1 inhibitors; iJAK – Janus kinase inhibitors. *MTX was prescribed to all patients in combination with GCs; during further observation, GCs were discontinued in 8 patients and they were transferred to MTX monotherapy; they were not prescribed bDMARDs.

cohort, it was found that tumor necrosis factor α inhibitors (iTNFα) were frequently prescribed (in 11% of cases). Currently, drugs of this group are used less frequently, they are used mainly in joint involvement, and therefore may not be represented in the St. Petersburg cohort, whose treatment analysis was conducted at the same time as enrolment in the study.

In the St. Petersburg cohort, 13 (31.7%) patients were taking colchicine (COL), which controlled disease manifestations and reduced the need for GCs in 9 of them. COL was prescribed at a dose of 0.5–2 mg/day in combination with non-steroidal anti-inflammatory drugs (NSAIDs) or GCs.

In the Moscow cohort, the course of the disease was complicated by the development of macrophage activation syndrome (MAS) in 6 patients. However, in 4 of them there was no significant delay in recognizing the disease – AOSD was diagnosed 1–5 months after the first clinical signs appeared. In 2 of these patients, MAS developed within the first months of the disease before the diagnosis of AOSD was made. In 2 patients, the onset of MAS at different stages of AOSD was triggered by noncompliance with the iIL6 therapeutic regimen. In 2 other patients, the diagnosis was delayed by 24 and 36 months, respectively, and the development of MAS was associated with prolonged inflammatory activity in the absence of adequate treatment. Two deaths were recorded in the Moscow cohort: one due to recurrent MAS and the second due to pulmonary embolism.

In the St. Petersburg cohort, MAS occurred in a patient with a systemic variant and polycyclic course of AOSD, GCs resistance and a history of ineffectiveness of synthetic DMARDs. The patient received canakinumab at a dose of 150 mg once every 4 weeks, but in the third month of therapy she developed MAS. This was probably due to an inadequate dose of the drug. Given the patient's body weight of 90 kg, the dose of the drug should have been 4 mg/kg according to the package leaflet, but not more than 300 mg every 4 weeks. The optimal dose of the drug for this patient was therefore 300 mg every 4 weeks. At the time MAS developed, she was in Ireland; after the episode had been resolved, she was prescribed iIL6. No lethal outcomes were recorded in this cohort.

Discussion. Epidemiological data indicate an increase in the incidence of AOSD in the last decade, which is certainly related to the good awareness of physicians about this rare pathology [5]. However, the small number of prospective observational studies and the lack of convincing results from randomized clinical trials raise many questions regarding the diagnosis and treatment of AOSD. In addition, this problem is less well addressed in the domestic literature than in the foreign literature. The present work is the first descriptive study of a cohort of patients with AOSD in the Russia.

The present study included 111 patients, which is comparable to the number of patients in other known national cohorts.

A comparison of our data with the results of other similar studies showed that there was no significant difference in the frequency of the various clinical manifestations during the course of the disease (Table 4).

The identification of systemic and articular subtypes of AOSD is based on data from A.T. Maria et al [9]. Fever (> 39°C), liver involvement , thrombocytopenia, elevated C reactive protein levels and hyperferritinemia appear to be associated with the systemic phenotype, while female sex, destructive arthritis and GCs dependence are features of the articular phenotype.

In attempting to identify the phenotypes in our cohort, we were faced with the need for a more thorough analysis of the dynamics of clinical manifestations. In addition, many patients were already receiving GCs or other therapy at the time of the study

Table 4. Spectrum of clinical manifestations of AOSD, according to various cohort studies [6–8]

Parameter	J. Pouchot et al., 1991 (n=62) [6]	H. Ichidaet al., 2014 (n=71) [8]	P. Ruscitti et al., 2016 (n=100) [7]	Almazov Research Center cohort (n=41)	NIIR cohort (n=70)
Mean age of the onset of AOSD, years	24	32	45	27,5	32
Women	45	65	66	73	70
Fever	100	99	100	100	100
Rash	54	79	78	75	74
Arthritis	94	93	86	80,5	63
Lymphadenopathy	75	61	57	51	45,7
Hepatosplenomegaly	55	48	79	51	52
Serositis	53	8	15	43,9	38,6
Sore throat	92	57	64	53	67

Note. Data are presented as % unless otherwise noted.

and were in remission. At the same time, it appears that most patients have a systemic phenotype at the onset of the disease and articular phenotype only emerges over the course of a long disease progression. It is known that a delay in diagnosis of more than 6 months, the absence of remission during initial therapy and male gender are predictors for the development of destructive arthritis and the chronic course of the disease [9]. Analyzing the AOSD phenotype appears to be an important task as it can determine the treatment tactics.

The monocyclic variant, which occurs in 19–44% of cases, is usually a systemic form of AOSD that is limited to a single episode of disease and leads to complete remission within a few weeks or months [10]. The low proportion of monocyclic variant (9.8%) in our study is not consistent with worldwide data and may be related to the specifics of the work of large centers. It is likely that patients with a monocyclic course, especially in the absence of arthritis, remain in the sight of specialists in infectious diseases and therapists due to fever of unknown origin and stay below the radar of rheumatologist.

The polycyclic variant, observed in 10–41% of patients, is characterized by recurrent systemic or articular exacerbations interspersed with periods of remission lasting from a few weeks to several years [10]. In the Moscow cohort, patients with a polycyclic course and a systemic form of AOSD occurred more frequently than in the St. Petersburg cohort. This could also explain more frequent development of MAS in the Moscow cohort, which in most cases is known to occur during systemic course of AOSD.

There are no generally recognized approaches for the treatment of AOSD, and the existing treatment methods have only a weak evidence base. The first line of therapy is usually NSAIDs in the diagnosis-seeking phase, in mild cases when there are no life-threatening manifestations. According to some data, the efficacy of NSAIDs in AOSD does not exceed 16% [11]. At the time of inclusion in our study, none of the patients were receiving NSAIDs monotherapy. The diagnostic search was completed in all patients and disease progression suggested a more active treatment tactic.

Patients with inadequate efficacy of NSAIDs and severe systemic manifestations are usually prescribed GCs. Most patients (74%) in our combined cohort used GCs in combination with DMARDs or biologics. Monotherapy with GCs was used in only 9% of cases, usually when MTX was poorly tolerated and the activity of AOSD was well controlled by low doses of GCs. The use of MTX is effective in 50–70% of patients with AOSD resistant to GCs monotherapy; moreover, the use of MTX allows a more effective reduction of the GCs dose [12]. According to some data, MTX therapy leads to a moderate reduction in arthritis manifestations in patients with JIA compared to placebo [13, 14].

bDMARDs are used to treat patients who are refractory to GCs and MTX therapy, iIL6 and iIL1 are considered to be most effective [15]. Until recently, iIL1 were not widely available in our country, mainly due to the extremely high cost of some drugs of this group. However, after the approval of the drug Anakinra in the Russian Federation in 2021, the range of biologic drugs prescribed for AOSD will change significantly in favor of iIL1.

The more frequent prescription of MTX in the Moscow cohort can be explained by the fact that some patients in St. Petersburg received COL. This drug is used in various autoinflammatory diseases, including familial Mediterranean fever and idiopathic recurrent pericarditis (IRP), as it can suppress the activation of the inflammasome and, accordingly, reduce the production of proinflammatory cytokines IL1 and IL18 [16]. It should be borne in mind that the existing criteria for AOSD and IRP are classificational and not diagnostic and are therefore not suitable for the differential diagnosis of these diseases. Given the similarity of clinical and laboratory findings between AOSD with serositis and IRP (often to the point of indistinguishability), COL has been used to treat patients with AOSD. There are descriptions of the successful use of COL in patients with a systemic inflammatory variant of AOSD when standard therapy, including bDMARDs, is ineffective or impossible to prescribe [16–20].

A total of 4 patients were not receiving therapy at the time of the survey, i.e. they achieved drug-free remission. In patients like these regular monitoring by a rheumatologist is recommended in order to stop any exacerbation promptly.

The mortality rate in the Moscow cohort was 2.8 %, which is comparable to the results from the Japanese cohort (3 %) and cohort from the USA (2.6 %) [21, 22]. MAS is a serious complication of AOSD and one of the main causes of death. According to Japanese authors, the mortality rate in the development of MAS

is 16%, the same ratio was found in our work – death in 1 (16.6%) of 6 patients with MAS.

It is known that patients who have previously had MAS are more likely to develop the disease again. More active administration of iIL1 in such cases will significantly improve the prognosis of the disease and reduce the incidence of death.

Conclusion. This work has several limitations. The type of data obtained dictated the study design (cross-sectional), which is an obvious weakness. Nevertheless, the information obtained gives an impression of patients with AOSD observed in real-world clinical practice and the type of therapy used and may be of practical use from this point of view. In a cross-sectional study, it is difficult to assess the dynamics of clinical manifestations, phenotype changes during the AOSD course, predictors of severe disease and the need to prescribe bDMARDs. Data analysis was performed simultaneously so that the therapy used at the time of enrolment in the study was optimal in each case. However, we know that the course of the disease changes; remission may be followed by an exacerbation that requires an adjustment of therapy.

Based on the work performed, we can draw a preliminary conclusion about the widespread problem of GCs dependence and resistance in patients with AOSD and about the limited therapeutic potential of MTX. According to the data obtained, up to 79.3% of patients with AOSD receive GCs for a long period of time, which is associated with a risk of complications.

The question of the optimal profile of bDMARD remains unresolved. The role of COL as a potential therapeutic option in certain clinical and immunological subtypes of AOSD merits further investigation.

This work will continue, and larger cohorts and more detailed analysis of various features will provide new information on the progression of AOSD and the efficacy of various treatments that may help to improve medical care for these patients.

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