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Takayasu's Arteritis: Monitoring of Clinical and Laboratory Activity in a Kyrgyz Cohort of Patients

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Abstract: Monitoring of clinical and laboratory Takayasu's arteritis (TAK) activity was carried out in 40 patients. Most of them were female patients (92.5%), of Kyrgyz nationality (97.5%), of young age (median - 32 years [24; 44]), with a disease duration of 7.5 years (median – (3.5; 12.5)), with the onset of the disease at 24 years (median –(19; 30)), with V anatomical type - (72.5%), which had vascular stage (77.5%), III grade (≥2) of vascular complications (37.5%), severe exacerbation (65%), with pronounced activity (92.5%) according to the EULAR criteria, high laboratory activity (accelerated ESR in 75% and increased hsCRP - in 65.71% of patients). The lesion of the common carotid (85%) and subclavian arteries (85%) prevailed, the renal arteries were the second most frequently (62.5%) affected vessels, with a predominance of bilateral stenosis (96.1%). During the 5.5 year- follow-up course, a statistically significant partial remission (according to the BVAS index) was achieved in only 12.5% of patients, while frequency of mild and severe exacerbations of the disease remained at the same level ($p > 0.05$). However, according to the EULAR criteria, there was a statistically significant decrease in the disease activity (from 92.5% to 65% cases) and an increase in the frequency of remission (from 2.5% to 27.5% cases), with the exception of episodes of relapses: major (12.5%) and minor ones (45%).

Keywords: Takayasu's Arteritis, Disease Activity, Angiography, Doppler Ultrasound, Tomography, Monitoring

1. Introduction

Takayasu's arteritis (TAK) belongs to the group of systemic vasculitis and is a chronic granulomatous arteritis with a predominant lesion of the aorta and its main branches [1]. The prevalence of the disease varies depending on the region of residence and ethnicity. So, for example, in Western Europe and the United States of America, the incidence of TAK varies from 2.6 to 33 cases, whereas in Asian countries - from 40 to 60 cases per 1,000,000 of adult population [2-12]. TAK most often occurs in the second or third decade of life, mostly in women of chilbearing age (80-90%) [13, 14].

The rarity of TAK, the undulating course, the variability of the lesion localization, the lack of standardized methods of laboratory and instrumental diagnostics creates additional difficulties in the management of patients in the actual clinical practice.

Unlike other Autoimmune inflammatory rheumatic diseases (AIIRD), TAK doesn't have any specific immunological markers. Routine laboratory tests of patients with TAK most often reveal increased levels of CRP and ESR, which does not always reflect the true severity of vascular inflammation [15]. According to a number of studies, elevated level of interleukin 6 (IL6), pentraxin 3 (PTX3), matrix metalloproteinase 9 (MMT9) and C4 binding protein (C4-bp) are observed in patients with high activity of TAK

[16, 17]. However, the significance of these indicators for assessing the disease activity and monitoring the course of TAK requires further studies [18].

The importance of instrumental examinations for establishing the diagnosis of TAK, clarifying the localization of damage and monitoring the disease activity is difficult to overestimate, however, not all of those can always be reliable. To diagnose and objectify the activity of TAK, various imaging modalities are used: ultrasound dopplerography (USDG), X-ray Angiography, Positron Emission Tomography (PET), Multispiral Computed Tomography (MCST) and Contrast-Enhanced Magnetic Resonance Angiography (CE-MRA), which allow to evaluate the structure and thickness of vessel wall, its relationship with the surrounding tissues, localization, degree and extent of the damage, as well as determine the therapeutic tactics. It should be noted that in a number of cases, the reliability of diagnostic tests in visualization of vessel wall inflammation is low, in particular, not all patients develop anatomical signs of vascular lesion during an active phase of disease [19].

In connection with the above, search for new, diagnostically reliable laboratory, as well as the imaging markers of disease activity becomes of great importance.

2. Objective

To evaluate of the diagnostic value of laboratory and instrumental research methods in monitoring of clinical and laboratory activity of TAK in Kyrgyz cohort of patients.

3. Material and Methods of Research

The study was based on 40 (30.53%) patients out of 131 with confirmed TAK diagnoses (according to the diagnostic criteria of the American College of Rheumatology-ACR, 1990) [20, 21], who were included in the monitoring of markers of clinical and laboratory activity and instrumental diagnostic methods: by ultrasound doppler up to 1 visit and ultrasound doppler and MSCT - panaortography in 1 visit.

Demographic data, clinical and angiographic features of the TAK course, and the results of laboratory studies were analyzed as per the approved protocol. All patients underwent a standard laboratory study of urine and blood (clinical and biochemical analyzes determining the levels of transaminases, serum creatinine and lipid spectrum).

To assess the laboratory activity of TAK, the level of highly sensitive C-reactive protein (hsCRP) was determined by immunoturbidimetric and chemiluminescent immunological analysis, and the level of IL6 was tested via enzyme-linked immunosorbent assay using mono- and polyclonal antibodies on analyzers "Immulite 2000 XPi" (Siemens, USA).

Mandatory instrumental examination included: electrocardiography (ECG), 24-hour Holter monitoring; echocardiography with visualization of the pericardium, heart valve apparatus, with measurement of systolic blood pressure (BP) in the pulmonary artery. If blood pressure in the pulmonary artery was ≥50 mm. hg., chest x-ray was performed, if indicated - computed tomography (CT) of the lungs with contrast.

To define the vessel's lesion, we used the findings from duplex doppler ultrasound of peripheral arteries in the color flow mapping mode and/or MSCT panaortography with contrast, in rare cases - X-ray angiography (performed on 3 patients), MSCT of coronary arteries (performed on 1 patient) or coronary angiography (performed on 2 patients). If necessary, MRI of the brain was performed (on 5 patients), in one case - with contrast.

MSCT - aortography was performed on a PHILIPS BRILLIANCE 64 SL apparatus with a 1.0 mm slice thickness. The scan covered area from the proximal parts of the brachiocephalic vessels to the level of bifurcation of the common femoral arteries. The native phase (without contrast) and the arterial phase (with intravenous injection of contrast agent Visipak 320) were filmed. The analysis of peripheral vascular lesions was carried out using the "AVA" program with the calculation of the vessel wall thickness, extent and degree of stenosis of the arterial bed. To assess the degree of narrowing of the arterial bed during MSCT - angiography, NASCET calculations (North American Symptomatic Carotid Endarterectomy Trial, 1991) were used, according to which stenoses classified as follows: mild (less than 50%), moderate (50-69%) and severe (70-99%) [22, 23].

The main limitation of our study was unavailability of MRI - angiography (with contrast enhancement) for technical reasons, due to which disease activity was judged according to the EULAR criteria (2018) [24]: clinical manifestations, ischemic complications and laboratory signs that were present in each patient at the time of examination, with defining of major and minor relapses, including remission of the disease.

The difference of imaging methods for assessing the localization and prevalence of anatomical alterations (thickening, stenosis, occlusion, dilatation, dissection, etc.) was due to the retrospectivity of the study and changes in technical support and clinical practice during a certan period of observation. However, the results of the ultrasound doppler were confirmed by at least one color doppler mapping.

The angiographic classification of R. Moriwaki et al. [25] was used to determine the anatomical type of vascular bed lesion. The involvement of the coronary and/or pulmonary arteries was designated as C (+) or P (+).

The disease activity was evaluated according to BVAS index, developed by R. Luqmani et al. [26] which includes three sections: clinical manifestations, laboratory and imaging parameters of the disease:

1) remission: (0–1 points): no signs of clinical activity and no need for therapy with a normal CRP level;
2) persistent disease: (50% of the baseline): a decrease in the clinical activity index as a result of treatment by 50% compared to the baseline;
3) limited disease/flare: (<5 points): new clinical signs of the disease with an increase in the total score to 5 points;
4) severe disease/flare: (> 6 points): involvement of vital

organs or systems in the inflammatory process (lungs, kidneys, central nervous system (CNS), cardiovascular system (CVS), which requires intensive treatment.

To characterize the clinical phases of TAK, the classification of R. Jefferson et al. was used. [27], according to which there are three stages:

Stage I (prepulseless, prevasculitis) - predominance of general symptoms (weakness, fever, fatigue, weight loss);

Stage II (vascular) - the formation of stenoses, occlusions, aneurysms and coarctations, clinically manifested by symptoms of vascular insufficiency (numbness of the upper and lower extremities, intermittent claudication, blurred vision, transient blindness, transient ischemic attacks, hemiplegia, convulsions, etc.);

Stage III (burned out) - the development of fibrosis or aneurysmal transformations of the arteries, which is often associated with remission of the disease (at this stage, a relapse of TAK cannot be outruled).

To determine the severity of complications and assess the prognosis of the disease, the classification of K. Ishikawa was used [28]. It is characterized by four most common complications: retinopathy, secondary arterial hypertension, aortic insufficiency and vascular aneurysm according to the following gradations: I - uncomplicated course of the disease with or without involvement of pulmonary arteries; IIA - 1 complication of mild/moderate severity; IIB – 1 severe complication; III - ≥2 complications.

Statistical Analysis

Statistical processing of the research results was carried out using the SPSS, 23 software (IBM, USA). The distribution of quantitative variables was analyzed using the Lilliefors normality criterion. Variables with a parametric distribution are presented as M ± SD, variables with a nonparametric distribution - as a as a median with an interquartile range (Me [25th; 75th percentile]). The significance of differences between groups was determined using a nonparametric Z-test. Differences were considered significant at $p<0.05$.

4. Result

The majority of patients were women (92.5%), of Kyrgyz ethnicity (97.5%), of young age – (median - 32 years old [24; 44], with a disease duration of 7.5 years [3.5; 12.5], with the onset of the disease at the age of 24 [19; 30], who were on inpatient treatment and were also observed as outpatients in NCIIM from January 2014 to September 2021 (Table 1).

Table 1. *General characteristics of followed up TAK patients before 1 visit (n = 40).*

Indices	Prior to 1st visit
Age of onset/age before 1st visit (Median)	24 [19;30]/32 [24;44]
Sex (f/m), n/%	37 (92.5)/3 (7.5)
Duration (Median) before 1st visit, years	7.5 [3.5;12.5]
Duration before diagnosis confirmation (Median) before 1st visit, years	4 [0.75;10]
Clinical stage, n/%:	
I (prepulseless, prevasculitis)	0 (0) 40
II (vascular)	31 (77.5) of 40
III (burned-out stage)	9 (22.5) of 40
Disease Activity (EULAR criteria), n/%:	
Active	37 (92.5)
Not active	3 (7.5)
Minor relapse	4 (10)
Major relapse	2 (5)
Remission	1 (2.5)
Sustained remission	0 (0)
Disease activity (BVAS index), n/%:	
Partial remission	0 (0) of 40
Complete remission	2 (5) of 40
Limited disease/ flare	12 (30) of 40
Severe disease/flare	26 (65) of 40
Severity of complications, n/%:	
0	1 (2.5)
1	4 (10) of 40
2A	10 (25) of 40
2B	10 (25) of 40
III	15 (37.5) of 40
Kidney damage n/%:	
RH	26 (65) of 40
IK	4 (15.38) of 26
Damage to the CVS, n/%:	29 (72.5) of 40
aortic valve insufficiency (AVI)	23 (79.3) of 29
AVI with minimal regurgitation	5 (17.24) of 29
AVI (mild)	7 (24.14) of 29
AVI (moderate)	11 (37.93) of 29
AVI (severe)	0 (0)
Arterial hypertension	3 (10.35) of 29
Coronariitis	1 (3.44) of 29
Myocardial fibrosis (PAF, VE)	2 (6.9) of 29
Frequency of PA damage (UD data), n/%:	
BCT	30 (75) of 40
CCA	34 (85) of 40
SCA	34 (85) of 40
VA	12 (30) of 40
AA and its branches	17 (42.5) of 40
CT	7 (41.18) of 17
SMA	10 (58.82) of 17
RA	25 (62.5) of 40
Laboratory indicators, n/%:	
1) accelerated ESR	30 (75) of 40
2) hsCPR	23 (65.71) of 35 examined patients
3) IL-6	1 (10) out of 10 examined patients

Note: TAK – Takaysu arteritis, AB – arterial bed, AT–anatomical type, RH–renovascular hypertension, IK–ischemic kidney, AH – arterial hypertension, VE – ventricular extrasystoles, CVS – cardiovascular system, AVI – aortic valve insuffiency, MR–minimal regurgitation, BCT – brachiocephalic trunk, CCA – common carotid artery, SCA–subclavian artery, VA – vertebral artery, PAF- paroxysmal atrial fibrillation, PA – peripheral artery, UD – ultrasound doppler AA – abdominal aorta, CT – celiac trunk, SMA –superior mesenteric artery, IMA – inferior mesenteric artery, RA –renal artery, hsCPR – highly sensitive C reactive protein, ESR– erythrocytes sedimentation rate, IL-6 – interleukin 6.

By anatomical type of vascular lesion, the patients were distributed as follows (Figure 1): type I was detected in 18 (13.85%) patients, type II (a and b) - in 24 (18.46%) patients, type III - in 2 (1.54 %), type IV - in 5 (3.85%) and type V - in 81 (63.3%), which indicated the prevalence of generalized and diffuse lesions of all parts of aorta.

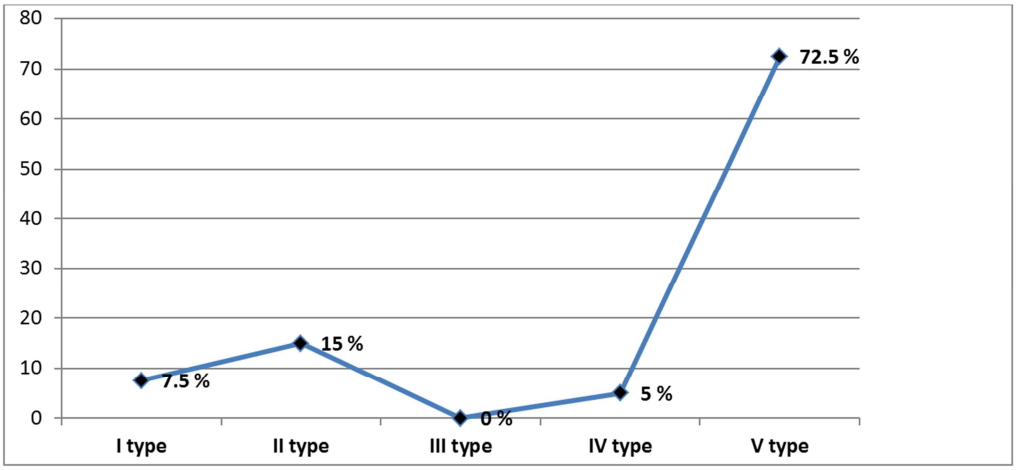

Figure 1. *Distribution of TAK patients by anatomical type of arterial lesion (n = 40).*

In accordance with the clinical classification, the majority of patients (31 or 77.5%) had vascular stage, characterized by the formation of stenoses, occlusions, aneurysms and coarctations (Table 1).

Only 2 (5%) patients fulfilled the criteria for partial remission of TAK according to the BVAS index; no cases of complete remission has been revealed. The majority of patients (65%) had a severe exacerbation and only (30%) had a mild exacerbation. The majority of patients (65%) had a severe disease flare and only (30%) had a mild relapse. And according to the EULAR criteria (2018), up to 1 visit, the overwhelming majority of patients (37 or 92.5%) had signs and symptoms of TAK activity, while inactivity was observed in only 3 (7.5%) patients. Achievement of remission was noted in only one patient (2.5%), sustained remission - in none. Analysis of laboratory markers of the disease showed an accelerated ESR and an increase in the level of hsCRP (75% and 65.71%, respectively) in most cases. As it turned out, high IL6 values were observed only in one case out of 10 examined patients. As can be seen from Table 1 the most frequently revealed lesions in the common carotid and subclavian arteries (equally) - in 34 (85%) cases, mainly in the form of stenosis (82.35% and 52.95%, respectively). The second most frequent lesion was the lesion of the renal arteries, which was present in 25 (62.5%) patients of 40, with a predominance of bilateral stenosis (96.1%). Involvement of the ascending aorta was observed in 23 (79.3%) of 29 patients with a prevalence of thickening of the intima-media complex (IMC) - in 23 (100%) and dilatation - in 18 (78.26%), which was the reason for the development of decompensated chronic heart failure in more than a third (37.93%) of patients.

As shown in Figure 2, according to USDG data in most patients, prior to 1st visit, the nature of vascular lesions was represented by stenosis, mainly of the renal arteries, common carotid arteries and brachiocephalic trunk (96.1%, 82.35% and 68.97%, respectively), in a quarter - by occlusion, mainly subclavian (29.4%) and vertebral arteries (25%). Whereas the dilatation of the arteries or their aneurysmal dilatation according to the ECHO data were visualized in the projection of the ascending aorta (in 78.26% and 13.04% of patients, respectively).

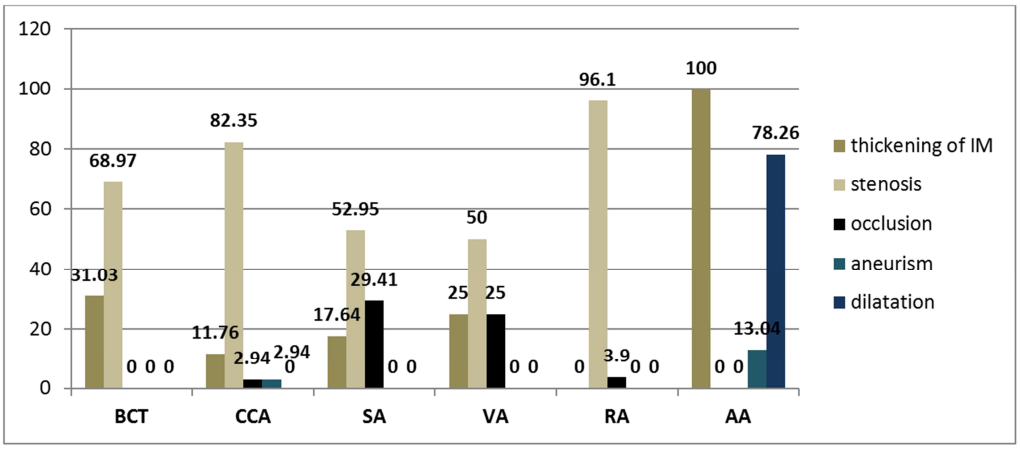

Figure 2. *Nature of lesion in the peripheral arterial bed according to Doppler ultrasound in the TAK patients before 1st visit (n=40).*

Note: BCT-brachiocephalic trunk, ASA – ascending aorta, IM – intima media, CCA – common carotid artery, SCA -subclavian artery, VA-vertebral artery, RA – renal artery, AA- abdominal aorta.

Analysis of the severity of complications and assessment of the prognosis of the disease according to the classification of K. Ishikawa demonstrated that 15 (37.5%) patients had ≥2 complications (III degree), which indicated a worse prognosis of the disease course, 1 mild / moderate and severe complication (2A and 2B) occurred with the same frequency - in 10 patients (25% and 25%, respectively).

To the 1st visit, the total duration of follow-up from the initial examination was 5.5 [2.4; 8.0] years, the age of the observed patients was 35 [26; 45.5] years, and the duration of the disease was 9 [4.75; 15.5] years.

Comparative analysis of monitoring of clinical and laboratory parameters and instrumental research methods showed that during 5.5 years of outpatient follow-up and inpatient treatment, reliably significant partial remission (according to the BVAS index) was achieved in only 12.5% out of 40 patients, at the same time, the frequency of mild and severe relapses of the disease remained at the same level (p> 0.05)., Table 2.

Table 2. *Comparative analysis of monitoring of clinical and laboratory manifestations and instrumental parameters (USDG) in patients with TAK (n= 40).*

Indicator	Before 1st visit	1st visit	p
Age (Median), years	32 [24;44]	35 [26;45.5]	-
Duration (Median), years	7.5 [3.5;12.5]	9 [4.75;15.5]	-
Severity of complication n/%:			
0	1 (2,5)	1 (2.5)	si
1	4 (10) of 40	4 (10) of 40	si
2A	10 (25) of 40	9 (22.5) of 40	si
2B	10 (25) of 40	4 (10) of 40	p<0.05
3	15 (37.5) of 40	22 (55) of 40	si
Disease activity (EULAR criteria), n/%:			
Active	37 (92.5)	26 (65)	p<0.05
Not active	3 (7.5)	14 (35)	p<0.05
Minor relapse	4 (10)	18 (45)	p<0.05
Major relapse	2 (5)	5 (12.5)	p<0.05
Remission	1 (2.5)	11 (27.5)	p<0.05
Sustained remission	0 (0)	2 (5)	p<0.05
Disease activity (BVAS), n/%:			
Complete remission	0 (0) of 40	0 (0) of 40	-
Partial remission	2 (5) of 40	5 (12.5) of 40	p<0.05
Severe disease flare	12 (30) of 40	7 (17.5) of 40	si
Limited disease flare	26 (65) of 40	28 (70) of 40	si
Kidney damage, n/%:			
RH	27 (67.5) of 40	27 (67.5) of 40	si
IK	2 (7.4) of 27	4 (14,81) of 27	si
CVS damage, n/%:	29 (72.5) of 40	31 (77.5) of 40	si
AVI:	23 (79.3) of 29	29 (93.56) of 31	si
AVI with minimal regurgitation	5 (17.24) of 29	10 (34.48) of 29	si
AVI (mild)	7 (24.14) of 29	6 (20.69) of 29	si
AVI (moderate)	11 (37.93) of 29	13 (44.83) of 29	si
AVI (severe)	0 (0)	0 (0)	-
Arteria hypertension	3 (10.35) of 29	1 (3.22) of 31	si
Coronariitis	1 (3.44) of 29	0 (0)	-
Myocardial fibrosis (PAF, VE)	2 (6.9) of 29	1 (3.22) of 31	si
PA (UD), n/%:			
BCT	30 (75) of 40	35 (87.5) of 40	si
CCA	34 (85) of 40	36 (90) of 40	si
SCA	34 (85) of 40	32 (80) of 40	si
VA	12 (30) of 40	15 (37.5) of 40	si
AA and her branches	17 (42.5) of 40	17 (42.5) of 40	si
CT	7 (41.18) of 17	7 (41.18) of 17	si
SMA	10 (58.82) of 17	10 (58.82) of 17	si
RA	25 (62.5) of 40	25 (62.5) of 40	si
Laboratory indicators, n/%:			
1) accelerated ESR	30 (75) of 40	30 (75) of 40	si
2) hsCPR	23 (65.71) of 35 examined patients	30 (75) of 40 examined patients	si
3) IL-6	1 (10) of 10 examined patients	12 (48) of 25 examined patients	si

Note: TAK – Takaysu arteritis, AB – arterial bed, AT – anatomical type, RH– renovascular hypertension, IK – ishemic kidney, AH – arterial hypertension, VE – ventricular extrasystoles, CVS – cardiovascular system, AVI – aortic valve insuffiency, MR–minimal regurgitation, BCT – brachiocephalic trunk, CCA – common carotid artery, SCA–subclavian artery, VA – vertebral artery, PAF- paroxysmal atrial fibrillation, PA – peripheral artery, AA – abdominal aorta, CT – celiac trunk, SMA –superior mesenteric artery, IMA – inferior mesenteric artery, RA –renal artery, hsCPR – highly sensitive C reactive protein, ESR– erythrocytes sedimentation rate, IL-6 – interleukin 6, si-statistically insignificant.

However, according to the EULAR criteria (2018), there was a significant decrease in TAK activity (from 92.5% to 65% of cases) and an increase in the frequency of remission (from 2.5% to 27.5% of cases), with the exception of episodes of disease relapses (large and small), which took place in 12.5% and 45% of cases, respectively (Figure 3).

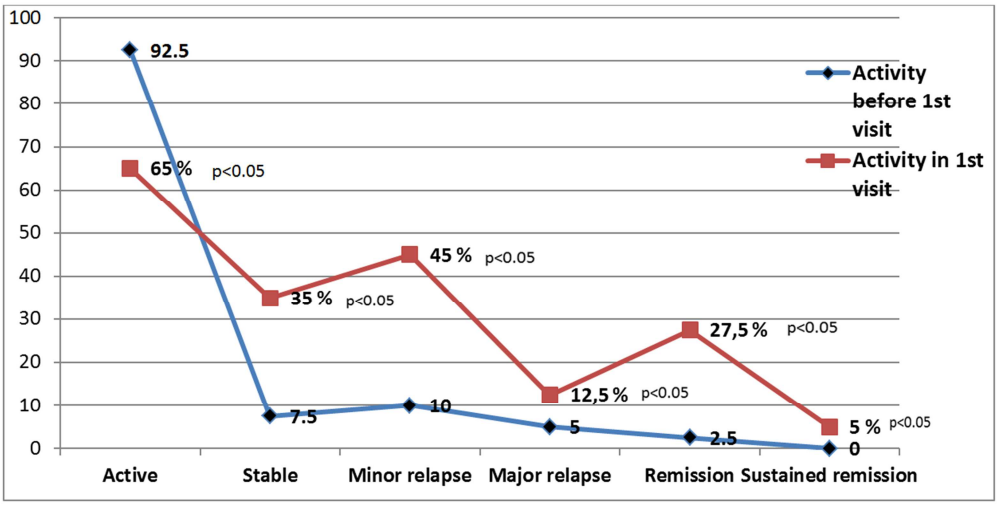

Figure 3. *Dynamics of disease activity according to EULAR criteria (2018) in 40 patients with TAK.*

According to K. Ishikawa's criteria (Table 2) of complications, attention was drawn to the insignificant (p> 0.05) progression of the degree and severity of complications (≥2), due to a decrease of the number of cases (p<0.05) in the groups of patients with one mild/moderate complication (2A) and one severe complication degree (2B) before 1st visit (from 25% to 10%).

At the 1st visit, according to USDG data, a predominant lesion of the brachiocephalic trunk (97.14%) in the form of IMC thickening (54.29%) and moderate stenosis (42.85%) were revealed (Figure 4). The second in frequency were stenotic changes in renal arteries (96.1) %. Dilation of the arterial wall or aneurysmal dilatation was most often observed in patients with lesions of the ascending aorta (68.97% and 10.34%, respectively), and irreversible occlusive alterations were mostly observed in the subclavian arteries (50%). Attention was drawn to an insignificant reduction (p>0.05) in cases with dilated and aneurysmal enlargement of the ascending aorta compared to the data prior to the 1st and during the 1st visit.

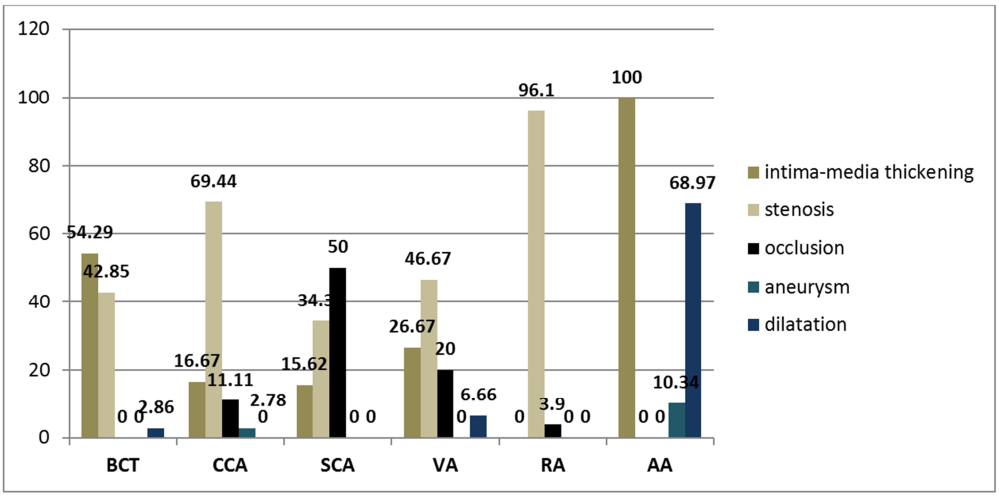

Figure 4. *Nature of arterial bed's lesion according to USDG of monitored patients in a 1st visit.*

Note: BCT – brachiocephalic trunk, ASA – ascending aorta, IMC– intima media complex, CCA – common carotid artery, SCA – subclavian artery, VA– vertebral artery, RA – renal artery.

At the 1st visit, according to MSCT panaortography, stenotic changes were mostly detected in the abdominal aorta - in all 40 (100%) patients, in the descending thoracic aorta - in 27 (67.5%) and subclavian arteries, mainly on the right - in 33 (82.5%), Table 3. Among the branches of the abdominal aorta, the most common involvement of the renal arteries, mainly the left (72.5%), superior mesenteric artery (70%) and celiac trunk (60%) were identified. By the nature of the lesion, minimal

stenosis was most often detected, mainly of the abdominal aorta and its branches (87.5%). Signs of critical stenosis and occlusion were found in the basin of the common carotid arteries, mainly on the left (52.17%) and subclavian arteries, mainly on the right (42.42%). As for the branches of the abdominal aorta, the phenomena of critical stenosis and occlusion were observed in the superior mesenteric artery (32.14%). According to the results of MSCT - panaortography, the brachial and mammary arteries were rarely involved (2.5% and 2.5%, respectively). There are practically no data on damage to the axillary arteries, which is probably due to the technical difficulties of visualizing this area.

Table 3. *Characteristics of arterial lesions in TAK patients according to MSCT data (n = 40).*

Involved arteries	Degree of vascular stenosis according to MRA data					
	MS (0-30%), n (%)	**MdS (30-49%), n (%)**	**SS (50-75%), n (%)**	**Critical stenosis (>75%), n (%)**	**Occlusion (100%), n (%)**	**Number of affected vessels, n (%)**
Aortic root	18 (45)	0 (0)	0 (0)	0 (0)	0 (0)	18 (45) of 40
ATA	21 (52.5)	0 (0)	0 (0)	0 (0)	0 (0)	21 (52.5) of 40
AA	19 (47.5)	0 (0)	0 (0)	0 (0)	0 (0)	19 (47.5) of 40
DTA	26 (96.3)	0 (0)	0 (0)	1 (3.7)	0 (0)	27 (67.5) of 40
BCT	17 (70.84)	1 (4.17)	2 (8.33)	2 (8.33)	2 (8.33)	24 (60) of 40
CCA:						
right	9 (37.5)	1 (4,17)	3 (12.5)	1 (4.17)	10 (41.66)	24 (60) of 40
left	3 (13.04)	2 (8.7)	4 (17.39)	2 (8.7)	12 (52.17)	23 (57.5) of 40
ICA:						
right	1 (33.33)	1 (33.33)	0 (0)	1 (33.33)	0 (0)	3 (7.5) of 40
left	0 (0)	0 (0)	3 (75)	1 (25)	0 (0)	4 (10) of 40
ECA:						
right	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (2.5) of 40
left	0 (0)	1 (50)	0 (0)	0 (0)	1 (50)	2 (5) of 40
SCA						
right	6 (18.19)	3 (9,09)	5 (15.15)	5 (15.5)	14 (42.42)	33 (82.5) of 40
left	9 (28.12)	1 (3.12)	5 (15.63)	6 (18.75)	11 (34.38)	32 (80) of 40
VA:						
right	2 (16.67)	0 (0)	4 (33.33)	1 (8.33)	5 (41.67)	12 (30) of 40
left	2 (22.22)	0 (0)	2 (22.22)	0 (0)	5 (55.56)	9 (22.5) of 40
AxA:						
Right	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Left	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
RRA:						
right	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
left	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.5) of 40
LRA:						
right	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (2.5) of 40
left	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)	1 (2.5) of 40
PA	0 (0)	0 (0)	2 (50)	0 (0)	2 (50)	4 (10) of 40
CA	2 (33.33)	0 (0)	1 (16.67)	2 (33.33)	1 (16.67)	6 (15.0) of 40
AA	35 (87.5)	0 (0)	2 (4.35)	2 (4.35)	1 (2.17)	40 (100) of 40
CT	5 (20.83)	4 (16.67)	5 (20.83)	4 (16.67)	6 (25)	24 (60) of 40
SMA	3 (10.71)	4 (14.29)	6 (21.43)	6 (21.43)	9 (32.14)	28 (70) of 40
IMA	1 (25)	0 (0)	0 (0)	0 (0)	3 (75)	4 (10) of 40
RA:						
right	3 (13.04)	2 (8.69)	6 (26.09)	6 (26.09)	6 (26.09)	23 (57.5) of 40
left	1 (3.45)	6 (20.69)	9 (31.03)	7 (24.14)	6 (20.69)	29 (72.5) of 40
ОПА	1 (33.33)	0 (0)	2 (66.67)	0 (0)	0 (0)	3 (7.5) of 40
СЗА	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (2.5) of 40
IA:						
right	0 (0)	0 (0)	0 (0)	0 (0)	3 (100)	3 (7.5) of 40
left	0 (0)	1 (33.33)	0 (0)	0 (0)	2 (66.67)	3 (7.5) of 40

Note: BCT – brachiocephalic trunk, FA- femoral artery, AA – abdominal aorta, ATA- ascending thoracic aorta, ICA – internal carotid artery, SMA –superior mesenteric artery AoA- arch of aorta, CCA– common carotid artery, CA– coronary artery, PA–pulmonary artery, MA– mammary artery, CHA–common hepatic artery, ECA–external carotid artery, SCA–subclavian artery, VA – vertebral artery, AxA-axillary artery, BA–brachial artery, RA–renal artery, SA–splenic artery, DTA–descending thoracic aorta, IMA – inferior mesenteric artery, IA–iliac artery, MS–mild stenosis, MdS–moderate stenosis, SS–severe stenosis, CS–critical stenosis, CT – celiac trunk.

5. Treatment

As shown in Figure 5, therapy before to the 1st visit included the use of glucocorticoids (GC) per os - in 36 (90%) and pulse therapy with methylprednisolone (MP) - in 9 (22.5%), methotrexate (MT) - in 34 (85 %), cyclophosphamide (CP) - in 3 (7.5%), hydroxychloroquine (HCC) - in 3 (7.5%) and biological therapy (BT) Tocilizumab (TCZ) - in 6 (15%).

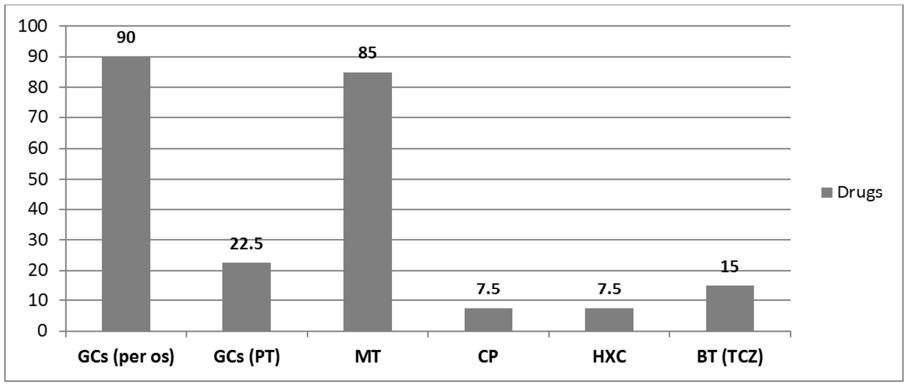

Figure 5. *Therapy of patients with TAK up to 1 visit (n = 40).*

Note: GCs–glucocorticoids, PT–pulse therapy, MT–methotrexate, CP– cyclophosphamide, HXC - hydroxychloroquine, BT – biological therapy, TCZ – tocilizumab.

Despite this therapy, there was no significant improvement in the frequency and nature of stenotic lesions of the arterial bed as per instrumental parameters ($p>0.05$), which was probably due to long duration of chronic inflammation (median - 9 years [4.75; 15.5], late diagnosis (median - 4 years [0.75;10]), the development of severe stenotic, occlusive and aneurysmal alterations, as well as the lack of timely adequate pathogenetic therapy at the onset of the disease.

6. Discussion

There is no "gold standard" in modern rheumatological practice for monitoring TAK activity at present. Increased levels of ESR and CPR most often revealed in a routine laboratory studies of TAK patients, do not always reflect the true severity of vascular inflammation [15]. In our study accelerated ESR was determined in 75% of patients, and an increase of hsCRP level - in 65.71% of cases. According to research based by Dagna et al., ESR and CRP values are less informative than the new biomarker pentraxin-3 (PTX3), which is produced by endothelial cells in response to inflammatory signals and is considered as an early laboratory marker of inflammatory activity in this disease [16, 29, 31]. In a number of other studies, increased levels of alternative biomarkers, such as IL6, leptin, ferritin, matrix metalloproteinase 9 (MMT9) and C4 binding protein (C4-BP) are associated with high TAK activity [16, 17]. However, their role as potential biomarkers of large vessels vasculitis remains uncertain, since there are no large-scale clinical studies confirming their diagnostic and clinical significance [18, 31, 32].

As a rule, clinical signs of TAK onset are nonspecific, which is one of the main reasons for the late diagnosis [3]. Thus, in our study, the time from the onset of the first symptoms to the diagnosis was 4 years (median [0.75; 10 years].

Even when the diagnosis is established, problems arise with the definition of the acute or "active" phase of the disease and the chronic stenotic phase, when symptoms or signs of the disease are the consequences of severe ischemia as a result of progressing narrowing of the arterial lumen [33]. According to the results of our study, at the time of initial examination, in most patients, the nature of vascular lesions was already represented by stenosis, predominantly of renal arteries (96.1%), common carotid arteries (82.35%) and brachiocephalic trunk (68.97%), a quarter - by occlusion, primarily subclavian (29.4%) and vertebral arteries (25%). Whereas dilatation of arteries (78.26%) and their aneurysmal changes (13.04%) were often noticed in ascending aorta. According to the EULAR (2018) criteria signs of disease activity were observed in the majority of patients (92.5%), while their absence - in only 3 (7.5%). Only 2 (5%) patients met the criteria for partial remission of TAK, in none of the cases complete remission was revealed. The majority of the patients (65%) had a major relapse of the disease and only (30%) had a minor one.

In other research works, when reviewing cases of patients with clinically inactive TAK, new angiographic signs of disease progression were found in 61% of cases, and surgical biopsy of the aorta revealed histological evidence of ongoing vascular inflammation in almost 44% of patients previously considered in remission [14]. As a result, there is growing evidence that more detailed invasive imaging is required to accurately determine disease activity. Therefore, the main clinical problem with TAK is to timely identify an active inflammatory process (the presence of vasculitis), when the disease is in the late stenotic phase and the activity of acute vasculitis may be minimal or absent [34]. For these cases, it is necessary to use contrast enhanced MR angiography. However, due to the interstitial distribution, traditional contrast agents based on gadolinium cannot be used to differentiate active inflammation of the vascular wall from fibrosis (after the injection of contrast agent fibrotic tissue is enhanced) [35]. In this regard, in clinical practice, a search for and implementation of new, reliable contrast agents is ongoing, the said agents could then be used in assessing the disease activity and in dynamic monitoring during certain therapy [36]. The main disadvantage of our study was the inability to conduct MRA (with contrast enhancement) due to

lack of software visualizing active process of arterial wall, current instrumental method objectively reveals inflammatory edema (increase in thickness), which indicates active vasculitis of large arteries [35, 37]. In connection with which, our research when evaluating disease activity according to EULAR (2018) criteria, mostly focused on clinical manifestations, ischemic complications and laboratory signs that every patient had the time of examination. As for MSCT- angiography, it visualizes the lesion of the vascular wall, more precisely, the state of the lumen of the artery, which can be useful in the diagnosis and subsequent monitoring of vascular changes, although it doesn't allow determining the presence of active vasculitis [38-41]. According to results of our study, MSCT-panaortography findings, stenotic changes were mostly revealed in the abdominal aorta (100%), the descending thoracic aorta (67.5%) and subclavian arteries (82.5%). Among the branches of the abdominal aorta, the most common renal arteries, mainly the left (72.5%), superior mesenteric artery (70%), and the celiac trunk (60%) were involved. By the nature of the lesion minimal stenosis was the most often detected, mainly of the abdominal aorta and its branches (87.5%). Signs of critical stenosis and occlusion were mainly found in the pool of common carotid arteries (52.17%) and subclavian arteries (42.42%). And among the branches of the abdominal aorta, the phenomena of critical stenosis and occlusion were observed in the superior mesenteric artery (32.14%). Comparative analysis of the arterial bed's lesion in our patients according to results of imaging (between USDG and MSCT angiography) demonstrated that the lesions of the subclavian arteries, the aortic arch, the descending thoracic and abdominal aorta, as well as the renal arteries ($p<0.05$) significantly more revealed by MSCT rather than USDG. At the same time, the involvement of the internal and external carotid arteries was more often determined by USDG (<0.05). Thus, when monitoring TAK patients, it is important to identify active inflammation, since active immunosuppressive therapy is required, but it is unclear if immunosuppression is effective in the late stage of the disease, when it is necessary to balance the risks and benefits [41].

In our study, despite active therapy, including the use of BT, there was no significant improvement in the frequency and the nature of the stenotic lesions of the arterial bed, imaging indicators, which was probably associated with a long duration of chronic inflammation, late diagnosis, the development of pronounced stenotic, occlusive and aneurysmal changes, as well as the lack of timely adequate pathogenetic therapy at the onset of the disease.

7. Conclusions

1) Among Kyrgyz TAK patients, diffuse and generalized lesions of all parts of the aorta and its branches were mainly observed (72.5%); vascular stage (77.5%); pronounced activity (92.5%); severe exacerbation (65%).
2) Mostly ≥2 complications (37.5%) prevailed, which indicated a worse prognosis of the course of the disease in the observed patients.
3) The laboratory activity of the disease was characterized mainly by high values of hsCRP (65.79%) and accelerated ESR (75%), much less - by an increased levels of IL6 (10%).
4) According to MSCT, stenotic changes were detected mainly in the abdominal aorta (100%), the descending thoracic aorta (67.5%) and subclavian arteries, mainly on the right (82.5%). Among the branches of the abdominal aorta, involvement of the renal arteries was most often noted, mainly the left (72.5%), superior mesenteric artery (70%) and celiac trunk (60%).
5) In a comparative analysis, according to MSCT data, lesions of the subclavian arteries, the aortic arch, the descending thoracic and abdominal aorta, as well as the renal arteries ($p<0.05$) were significantly more often detected compared with the results of USDG. At the same time, the involvement of the internal and external carotid arteries was more often determined by USDG ($p<0.05$).
6) The obtained preliminary results of the study indicate the absence of significant positive dynamics of clinical, laboratory manifestations and of the course of TAK on a standard therapy, which is probably associated with a longer duration of chronic inflammation, late diagnosis, the development of pronounced stenotic, occlusive and aneurysmal changes, as well as the lack of timely adequate pathogenetic therapy at the onset of the disease.

Author Contributions

Koilubaeva Gulazyk Malikovna, conceived and designed the analysis; conducted monitoring of patients (the clinical and laboratory data and treatment), performed the analysis, wrote the paper; Bolotbekova Altynai Maratovna, collected the data and assisted in monitoring patients; Sarybaev Akbai Shogaipovich, provided assistance in the approval of the scientific thesis; Chukubaev Marat Abdyganovich, participated in instrumental research (made a data conclusion of the computed tomography); Turdukulov Zamirbek Ergeshevich, participated in instrumental research (conducted the computed tomography); Usupbaeva Dinara Abulmeizovna, participated in instrumental method of the research (made a data conclusion of the doppler ultrasound); Turusbekova Aijan Kemelovna, participated in imaging methods (performed the doppler ultrasound); Egorova Olga Nikolaevna, advised on the design of the article; Tarasova Galina Michailovna, participated in the design of the study.

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All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors.

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