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Dynamics of Indicators of Immune Status and Endothelial Function in Patients with Nonspecific Aortoarteritis on the Bacround of Combined Therahy with Eqvator and Plavix

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Annotation: The article examines the results of the study of the immune status in patients with nonspecific aortoarteritis in the dynamics of combined therapy. Calcium antagonists, ACE inhibitors and antiplatelet agents. Data on the undeniable advantages of combined antihypertensive therapy with the equator and thesseron, affecting a large number of the most diverse links in the pathogenesis of NAA - the activity of immune inflammation, endothelial dysfunction, hypertrophy of the myocardium and vascular wall.

Keywords: nonspecific aortoarteriitis, the immune status.

Introduction. Nonspecific aortoarteritis (NAA) is a systemic vasculitis with a predominant lesion of the aorta and its branches. According to the Chapel Hill Consensus Conference (1994) classification of vasculitis, this disease is defined as "granulomatous inflammation of the aorta and its main branches". This disease is also known as "Takayasu disease", "lack of pulse disease", "arteritis of young women", "arteritis of the aortic arch", "panarteritis", "aortic syndrome". It is noted that NAA occurs mainly in young women (the ratio of incidence of women and men is 8:1), usually at the age of 20 to 30 years. At the same time, the ratio between men and women in Russia ranges from 1: 2.4 to 1.71 [8-10]. The incidence of non-specific aortoarteritis is 2.6 cases per 1 million population [11] with a possible increase, since data on incidence and prevalence are limited. At the same time, in East Asia, its frequency is 100 times higher. This is a rare autoimmune disease characterized by granulomatous inflammation of the aorta and main arteries [1]. The first reports of this disease appeared in the middle of the XIX century. However, the disease was previously described by G. B. Morgagni and William Savory [2,3].

Methodology

In 1761, G. B. Morgagni described the absence of a pulse on the radial artery in a 40-year-old woman for at least 6 years before death. At the autopsy, the radial arteries were not changed, and there was a widening of the proximal part of the aorta in combination with stenosis of the distal sections. The inner layer of the aorta was yellow and contained calcinates [2]. In 1856, William Savory [3] provided a convincing description of the disease in a 22-year-old woman admitted to St Bartholomew's hospital (London). The patient suffered from undefined symptoms for 5 years, later seizures began to occur, and the pulse was not detected on the vessels of the neck, head and upper extremities. During her stay in the hospital, which was 13 months, she became blind in her left eye, and a large ulcer appeared on the scalp. Post-mortem examination revealed a thickening and narrowing of the aorta and vessels of the aortic arch - the vessels felt like a tight rope. According to William Savory, the main cause of the described condition is probably inflammation of the inner layer of the arterial wall, the disease progresses over a long period of time and may have an asymptomatic course.Non-specific aortoarteritis (NAA) is one of the rare vascular diseases

characterized by circulatory disorders in various arterial basins, which causes a variety of clinical manifestations of this pathology. A feature of the clinical course of the disease is the formation of various syndromes depending on the degree and localization of vascular lesions [6, 8]. It is known that timely and early start of treatment prevents the progression of the disease and the development of complications. The leading clinical syndrome of this disease is arterial hypertension (AH), which is observed in about 70% of patients. Hypertension in patients with non-specific aortoarteritis is a consequence of immune inflammation of large and medium-sized arteries, contributes to the remodeling of the heart and blood vessels, and the formation of cardiovascular complications. Research in recent years has established that the endothelial layer of the vascular wall is damaged during the formation of cardiovascular diseases at the earliest stages of the pathogenesis of NAA. [7, 9, 12].According to the literature it is known that calcium antagonists and ACE inhibitors have a vasoprotective effect, cause regression of vascular remodeling [2, 3, 5], contribute to correction of endothelial dysfunction by reducing the creation of angiotensin II, reduce the activity of monocytes-macrophages, inhibit the activation of adhesion molecules and mediators of inflammation, migration of smooth muscle cells in the lesion inflammatory lesions, growth of smooth muscle cells of the vascular wall [10, 11, 13]. These processes underlie the anti-inflammatory and angioprotective effects of equator), which is a fixed combination of the angiotensin-converting enzyme inhibitor lisinopril, with the calcium antagonist amlodipine. The presence of a sulfhydryl group in the structure of the equator molecule determines the ability of the drug to counteract oxidative stress, the elimination of reactive oxygen species and other free radicals that initiate the development of immune-inflammatory processes in the vascular wall, and the formation of endothelial dysfunction. This combination is pathophysiologically and clinically justified, highly effective, and has independent evidence of a favorable effect on the cardiovascular prognosis. The fixed combination of lisinopril with amlodipine appeared in clinical practice in Uzbekistan as the first of this combination and in just a few years has taken a fairly strong place among modern therapeutic approaches for hypertension. Both components belong to the first-line treatment of hypertension with a good level of evidence for positive effects on cardiovascular prognosis[1, 4]. Plavix (clopidogrel) is an antiplatelet drug, a representative of the thienopyridine class. By blocking platelet receptors to adenosine diphosphate, it reduces their activity and ability to aggregate, and ultimately reduces the risk of serious thrombotic complications in various manifestations of stenotic diseases of the aorta and arteries.

We studied the dynamics of immune status indicators in patients with NAA on the background of combined therapy with equator and plavix. Taking into account the role of immune disorders in the progression of endothelial dysfunction in patients with NAA, a control study of immune status indicators after equator monotherapy and a combination of plavix with equator was conducted. 37 patients with NAA were studied. The control group included 30 healthy donors: 12 men and 18 women aged 22 to 38 years, with an average age of 24.2±6.3 years. All patients were randomly selected into two groups: the first group consisted of 19 NAA patients who took equator at a dose of: lisinopril 10 mg / day + amlodipine 5 mg / day and plavix (clopidogrel) 75 mg/day; the second group included patients (18 people) whose therapy included taking equator at a dose of: lisinopril 10 mg/day + amlodipine 5 mg/day. The duration of therapy was 6 months. All examined patients with NAA received pathogenetic therapy with prednisone at a dose of 40 mg / day, respectively, with the degree of activity of the disease.

Results. Evaluation of the effectiveness of the influence of equator and antiaggregantaplavix on the immune status, endothelial function, vascular wall thrombosis and Central hemodynamics of patients with NAA with II degree of hypertension showed the following results.

After 6 months of therapy with equator inclusion in patients with NAA with II art. ED showed a significant decrease in proinflammatorycytokinemia: (the level of TNF was 103.1±10.2 pg / ml; IL-1β - 111.4±12.2 PG / ml, IL-6-44.8±5.1 pg/ml). The use of the equator+plavix combination was

accompanied by a potentiation of anti-inflammatory activity, which was manifested by a decrease of approximately 2 times the serum concentration of the studied cytokines(table 1).

Table 1. Dynamics of the content of Pro-inflammatory cytokines inblood serum of patients with NAA with III-IV degree of ED on the background of therapy

Indicator	Groups of surveyed people(n=37)			
	Control(n=30)	Beforetreatment(n=37)	Therapy with the equator (n=18)	Therapy with the equator +plavix(n=19)
TNFapg / ml	39,4±3,6	170,4±9,2	103,1±10,2	66,3±5,8
IL-1β pg / ml	36,4±4,1	175,9±12,3	111,4±12,2	56,3±4,1
IL-6 pg / ml	17,8±3,9	80,1±6,2	44,8±5,1	23,1±3,8

In patients with NAA with grade III-IV ED, the use of equator alone against the background of basic prednisone therapy significantly reduced the hyperproduction of proinflammatorycytokines.There was also a decrease in TNF content by 39.5%, IL-1β by 36.7%, and IL-6 by 44.1%. More significant changes in the level of proinflammatorycytokinemia were achieved in the group of patients receiving equator+plavix therapy, the content of TNF decreased by 61.1%, IL-1β - by 68%, IL-6 – by 71.2% in comparison with the indicators before treatment. When evaluating the effect of complex therapy with the inclusion of equator and plavix on the concentration of proinflammatory cytokines in patients with different disease duration, it was found that equator in comparison with the combination of equator and plavix has a lower activity of influence on the studied cytokines in patients with NAA with a history of disease less than 1 year. Equator+plavix therapy in patients of this group led to a decrease in proinflammatorycytokinemia to the level of control, the use of equator alone was accompanied by a significant decrease in the content of TNF, IL-1β, and IL-6. With a history of NAA from 1 to 3 years, only complex therapy (equator+plavix) had a significant corrective effect on proinflammatorycytokineemia, while it should be noted that normalization of the level of proinflammatory cytokines in patients of this group was not achieved.

There was a significant corrective effect of equator and baseline therapy on the hyperproduction of anti-inflammatory cytokines in patients with NAA with grade II ED, characterized by a significant decrease in the concentration of IL-4, IL-10 and Tfrß1 (to 48.1±4.8 PG / ml; 26.5±1.8 PG/ml and 68.6±4.2 PG / ml, respectively). The use of equator+plavix was accompanied by a significant increase in therapeutic activity, achieving a lower concentration of anti-inflammatory cytokines (IL-4-37.2±3.9 PG / ml, IL-10-18.1±2.1 PG / ml, TFR-β1-60.8±4.1 PG/ml.).

In patients with III-IV degree of ED severity, the appointment of both equator and equator+plavix combination was accompanied by less significant dynamics of these indicators. Thus, after 6 months of combined therapy (equator+plavix +prednisone), the content of IL-4, IL-10 and TFR-β1, respectively, was: 62.1±3.8 PG / ml ($p<0.05$), 27.2±2.1 PG/ml ($p<0.05$) and 76.9±3.8 PG/ml ($p<0.05$) (table 2).

Table 2. Dynamics of the content of cytokines of anti-inflammatory action in the blood serum of patients with NAA with III-IV degree of ED on the background of therapy

Indicator	Groups of surveyed people (n=37)			
	Control(n=30)	Beforetreatment (n=37)	Therapy with The equator (n=18)	Therapy with the equator+plavix(n=19)
IL-4 PG / ml	23,2±4,5	88,8±4,2	75,9±3,6	62,1±3,8
IL-10 PG / ml	13,4±3,6	47,2±2,3	38,2±2,9	27,2±2,1
TFR-β1pg/ml	40,9±6,9	99,8±3,2	89,2±2,8	76,9±3,8

At the same time, treatment only with equator while taking prednisone had significantly less corrective effect on the level of cytokines studied. The effectiveness of the studied drugs on the level of IL-4, IL-10 and TFR-β1 also depends on the duration of the course of NAA. With the duration of NAA less than 1 year, equator therapy caused a significant decrease in the level of these cytokines. Complex therapy equator+plavix led to normalization of the serum spectrum of anti-inflammatory cytokines, with the duration of the disease from 1 to 3 years, only complex therapy (equator+plavix) significantly reduced the hyperproduction of IL-4, IL-10 and TFR-β1(by 34.2%, 18.3% and 44.6%, respectively).

In our research, we studied the effect of combined equator and plavix therapy on the performance of functional vascular samples of patients with hypertension in NAA.

As a result of the conducted studies, an increase in the value of endothelium-dependent vasodilation(ESDD) of the brachial artery in patients with NAA after 6 months of equator therapy and equator +plavix combination against the background of basic prednisone therapy was revealed, at the same time, a more pronounced dynamics was observed in patients with NAA with grade II ED in comparison with indicators at the III and IV stages of ED.At the III-IV degree of ED, monotherapy with equator did not have a significant effect on the studied parameters.The most pronounced changes in the functional state of the endothelium against the background of equator monotherapy were achieved in patients with NAA with grade II ED, with a duration of AH less than 1 year.The combined use of plavix and equator was accompanied by a significant increase in the vasoprotective effect of therapy, what was shown by stopping signs of endothelial vascular dysfunction in patients with NAA with II degree of endothelial functional disorders and their significant reduction in the III-IV degree of ED.

The average value of ESRD after equator treatment in NAA patients with grade II ED was 7.1 ±0.9%, $p<0.05$. The combined use of a fixed combination of lisinopril and amlodipine with the antiplatelet agent plavix resulted in a significantly greater increase in the ESRD value (8.2±0.8%>) in comparison with equator monotherapy.

Analysis of the results of tests to assess the vasomotor activity of the brachial artery found that in patients with NAA with grade II ED, equator therapy and the combination of equator+plavix was accompanied by an increase in the growth of flow rates in the brachial artery, the value of these indicators was respectively equal to: 165.8±23.2 cm/min, $p<0.05$, 159.9±19.8 cm/min, $p<0.05$, and 188.3±18.5 cm/min, $p<0.05$. In the III - IV stages of ED, complex therapy with equator+plavix in comparison with equator therapy had a more pronounced effect on the studied parameters. Thus, equator therapy was characterized by an increase in ESRD to 3.9±1.3%, i.e. there was only a tendency to increase ESRD, against the background of equator+plavix therapy, this indicator was 6.9±1.2%, $p<0.05$, respectively. The increase in blood flow rate was also significantly higher in patients after complex therapy.

Control duplex scanning of the common carotid arteries in the groups of examined patients showed the following results.

It was established that equator therapy was accompanied by a pronounced effect on the vascular wall remodeling process, which was manifested by a significant decrease in TIM of the carotid arteries after 6 months of therapy in patients with NAA from stage II. ED up to 0.86 ± 0.01 mm; during combination therapy, TIM decreased to 0.78 ± 0.02 mm. In patients with NAA with IV tbsp. ED administration of the equator led to a decrease in TIM by 5.2%, combined treatment by 14.5% compared with the initial data. Studies have shown that the equator and Plavix have, along with anti-inflammatory efficacy, a corrective effect on ED and CCC remodeling processes.

Thus, the studies showed that the appointment of the equator to patients with NAA against the background of basic glucocorticosteroid therapy is accompanied by greater effectiveness of the corrective effect on the indicators of immune status, compared with the use of the equator alone, while the effectiveness of treatment depends on the severity of ED and the duration of the history of NAA; The highest activity of therapy was observed in patients with NAA with signs of ED of II severity and

a history of less than 1 year. In patients with NAA with II degree of ED with a duration of hypertension of up to 1 year, the indicators of immune status after monotherapy with an equator did not differ from the norm. With II degree ED in patients with a NAA duration of 1 to 3 years, against the background of the use of the equator, correction of immune disorders was achieved. An increase in the anti-inflammatory effect of therapy with the combined use of drugs was noted, which was manifested by a decrease in the activity of the monocytic-macrophage immunity, correction of cytokine profile disorders in patients with NAA with III-IV degree of ED, and relief of immune disorders in patients with NAA with signs of grade II ED.

Conclusion. Among the variety of causes of the development of arterial hypertension, nonspecific aortoarteritis takes a special place [1; p. 9-12.31; p. lesions by the process of various vascular pools and, finally, underestimation of treatment results are important components that require an urgent solution [45; p.1281-1357]. Recent decades have been marked by the accumulation of a significant amount of knowledge on the problems of diagnosis and treatment of NAA. NAA is considered as a multifactorial pathology, the pathogenesis of arterial hypertension in this case, is closely associated with progressive modeling of the heart and blood vessels, in which the endothelial dysfunction of the vascular bed plays a significant role. The leading role in the pathogenesis of NAA is played by the immune mechanisms of cardiovascular remodeling. It is known that it is not always possible to improve the prognosis and reduce the risk of developing cardiovascular complications, including hypertension, since pharmacotherapy is often symptomatic, does not affect the mechanisms of DE formation and, therefore, does not restore normal endothelium-dependent reactions [24; .16-18,45; p.1281-1357]. Therefore, studies of the immune mechanisms of DE progression in NAA are promising, as well as the study of anti-inflammatory and vasoprotective activity of calcium antagonists, ACE inhibitors and antiplatelet agents used in the treatment of NAA. This will make it possible to choose the most effective drug, avoid additional drug loading on the patient, and will contribute to increasing patient adherence to treatment and influence the prognosis of the disease. All of the above determined the purpose and objectives of the study.

The aim of the study is to determine endothelial dysfunction and immunological parameters before and after treatment in patients with nonspecific aortoarteritis.

The object of the study was 74 patients with a diagnosis of nonspecific aortoarteritis with arterial hypertension and 30 healthy subjects who were monitored in the Bukhara regional multidisciplinary medical center. Patients were divided into 2 groups, women comprised 49 patients, men 25 patients. The average age was 27.5 ± 4.1. The control group was 30 healthy people, 12 men and 18 women aged 22 to 38 years, the average age was 24.2 ± 6.3 years. The determination of pro (TNFα, IL-1β, IL-6, IL-8, INF-γ) and anti-inflammatory cytokines (IL-4, IL-10, TGF-β1) was performed before and after treatment.

The state of endothelial function was evaluated by the concentration of ET-1 in the blood, determining the degree of ESVD of the brachial artery.

It is known that endothelium is both a target and a mediator of cardiovascular diseases, changes in its functions are already observed in the early stages of the disease [20; p.22-27.39; p.51-55]. Consequently, the use of diagnostic tests to detect early changes in blood vessels makes it possible to identify patients with a high risk of progression of vascular diseases and monitor therapy. Carrying out such studies has allowed to develop differentiated approaches to the treatment of NAA, to improve prognosis. Currently, the most common method for assessing endothelial function is to study the vasomotor response of the brachial artery using ultrasound [34; p.22.44; p.61-67]. The advantage of this method is the availability and non-invasiveness of the conduct.

Determining the severity of ED was performed with a sample of reactive hyperemia. Arterial hyperemia caused a breakdown of reactive hyperemia in the brachial artery; in patients with NAA, it was significantly less than in the control group — 6.3 ± 1.3% and 10.6 ± 2.1%, respectively. In patients with NAA, changes in blood flow velocity caused by reactive hyperemia were determined less significantly (below the control level, on average, 35% change), in patients with NAA, blood flow velocity changed by 1.5 times less than in the control group.

According to the literature [50; p. 1111-1115.71; p. 276-285], the normal response of the brachial artery in a sample with reactive hyperemia is considered to be a vasodilator response of more than 10%; vasodilation less than 10%, as well as paradoxical vasoconstriction indicate a violation of the vasomotor function of the endothelium. In our study, EDV more than 10% was not registered in any patient with NAA, which indicates the presence of DE in the examined patients. All patients, depending on the indices of the cuff test, were divided into 3 groups. The criterion of randomization was the severity of DE, determined by the magnitude of the endothelium-dependent vasodilation of the brachial artery [91; p.32-39]. The results obtained in patients after the examination showed vasodilator dysfunction of the II degree, moderate severity (42%) and in severe III degree, a vasodilatory disorder (58%).

As a marker of endothelial function in cardiovascular pathology, the level of endothelial peptides in blood plasma was considered. Endothelial peptides - endothelin - are one of the most powerful vasoactive substances [93; p.2184-2190]. One of the representatives of this family is ET-1, released by the endothelium of the vascular bed, in which it is present as a modulator of vascular tone, cell proliferation [94; p. 355-341.96; p. 099-916].

It is known that endothelin is capable of exerting both a vasoconstrictive effect [56; p. 614-796] and affect various local metabolic processes. Great importance is attached to the ability of endothelin to control endothelium-independent vasoconstriction in violation of the mechanical properties of the endothelium [56; p. 694-716].

Studies of the level of ET-1 showed an increase in its concentration in patients with NAA compared to healthy ones. Stage III hypertension with NAA of ET-1 content showed a significantly higher level. (15.29 ± 1.2 ng / L; $p < 0.01$), it is associated that this group included patients with a severe degree of DE.

With prolonged exposure to damaging factors, such as inflammation, hemodynamic load, a gradual occurs. The depletion and distortion of the compensatory "dilating" ability of the endothelium and the primary "response" of endothelial cells to conventional stimuli is the production of vasoconstrictor mediators, including endothelin-1, the hyperproduction of which causes the development of vasoconstriction and proliferation, causing the progression of endothelial dysfunction [23; 20.107; p.1671-1674]. It should be emphasized that the expression of preproendothelin and increased release of the active peptide can stimulate various humoral factors, in particular ty angiotensin II, IL-1, TNFα. Therefore, it was of interest to study the parallels between the pro-inflammatory cytokines and the expression of ET-1.

When assessing the functional state of the endothelium, intimal media thickness was determined, leading to vascular wall remodeling for ED of various severity, a high level of TIM was determined above the corresponding indices in the control group ($p < 0.01$). A high level of TIM was found in the group of patients with grade III ED, the values were 1.1 ± 0.03 mm, and in patients with the control group, the indicators were 0.65 ± 0.09 mm.

Studies have shown that the severity of vascular endothelial dysfunction directly correlates with changes in TIM, the most pronounced signs of vascular remodeling occurred in patients with NAA with a severe degree of endothelial dysfunction.

Thus, studies have shown the presence of endothelial dysfunction in patients with NAA, progressing with severity of hypertension AH.

Since one of the main functions of the endothelium is immune, including the presentation of antigens to immunocompetent cells, the secretion of cytokines, adhesion molecules, etc. [16; p.114-118] on the vascular wall, we studied the relationship between indicators of immune status and endothelial function in patients with NAA.

In recent years, the attention of researchers has been attracted by the study of the cytokine status in NAA. It has been established that cytokines enhance the prothrombogenic and vasoconstrictor activity of the endothelium, stimulate the expression of adhesive molecules for activated leukocytes and platelets, and cause vascular wall infiltration by inflammatory cells [13; p.478-486.19; p.121-123.31; p.148- 151]. Evidence has been obtained that inflammatory mediators - cytokines - are markers of endothelial dysfunction [117; p. 1015-1023].

Researchers of this problem attach great importance to the role of pro- and anti-inflammatory cytokines in this

process, which is especially important for NAA, in which the damage to the vascular bed is systemic. We have studied the content of a wider range of pro-cytokines (TNF-a, IL-1β, IL- 6, IL-8, INF-γ) and anti-inflammatory effects (IL-4, IL-10, TGF-β1) in the serum of patients with NAA, depending on the severity of hypertension and ED. Studies have revealed an increase in the content of TNFα, IL-1β, IL-6, IL-8, INF-γ in the blood serum of patients with NAA, increasing with the severity of ED and art. AH. It is known that TNFα has a local effect on the vascular wall, including the expression of adhesion molecules on the surface of vascular endothelial cells, resulting in the adhesion of neutrophils, monocytes, lymphocytes with the development of inflammatory vascular wall infiltration [22; p. 72-77]. When examining the level of IL-1β in patients with NAA, the following results were obtained. A moderate increase in the level of IL-1β in patients with NAA was noted. Assessment of the content of IL-1β in the blood serum of patients with varying severity of hypertension with NAA showed its maximum concentration in the group of patients with NAA with hypertension IIIst. IL-1β is synthesized by macrophages and monocytes, as well as vascular endothelial cells. IL-1β exhibits a wide range of local and systemic effects, which include: activation of T and B lymphocytes, induction of the synthesis of adhesion molecules and IL-8. Therefore, an increase in IL-1β is an integral mechanism for the progression of endothelial dysfunction [62; p. 373-376].

In patients with NAA, we determined an increase in the level of IL-6 compared with the control. Studying the concentration of IL-6 in patients with NAA of varying severity of hypertension showed its highest content in NAA and hypertension of III severity. IL-6 is the main cytokine that stimulates the production of secondary inflammatory participants in the hepatocytes - acute phase proteins: C-reactive protein (CRP), amyloid A, apolipoprotein-α, fibrinogen, complement components [68; p. 2296-2304]). These factors trigger a cascade of local and systemic inflammatory reactions. An important property of IL-6 is the effect on the procoagulant activity of blood.

In patients with serum HAA, there is a high degree of correlation between the indicators of endothelial function and pro-inflammatory cytokines. A direct correlation between the level of ET-1-cytokines causing inflammation was determined, the inverse relationship was established between the value of EDVD and the concentration of these cytokines, which is due to the properties of TNF-α, IL-1 IL-8, INF-γ, induce the development and progression of endothelial dysfunction.

There are insufficient data in the literature to evaluate the content of anti-inflammatory cytokines in patients with NAA. Therefore, we studied the content of anti-inflammatory cytokines IL-4, IL-10, TGF-β1 in the blood serum of patients with NAA.

In patients with NAA with hypertension III tbsp. depending on the clinical symptoms, it was found that the highest level of IL-4 was found. IL-4 and IL-1β ($r = 0.64$, $p < 0.01$), IL-4 and TNFα ($r = 0.51$, $p < 0.05$), IL-4 and IL-6 ($r = 0.47$, $p < 0.05$) a direct correlation was determined between cytokine parameters.

Characteristic for cytokines is: pleiotropy, overlapping and overlapping effects, the interaction of different cytokines in cascades of a single regulatory system. The cascading nature of the action of cytokines is explained by the fact that one cytokine affects the production of another [23; p.10-20.53; p.973-981]. IL-4 is capable of inhibiting the secretion of IL-1β and TNFα by macrophages. This leads to an increase in the level of IL-4 in response to the overproduction of IL-1β and TNFα, with the progression of DE in patients with NAA.

In patients with NAA, an increase in the number of anti-inflammatory cytokines was detected, a high degree of correlation between the indicators of endothelial function and the level of anti-inflammatory cytokines in the blood serum of NAA was determined. A direct correlation was established between the concentration of IL-4, the level of ET-1 in the blood serum of patients with NAA, the inverse relationship was between EDVD and IL-4.

There is practically no information in the literature on the activity of anti-inflammatory cytokines (IL-10, TGF-β1) and their role in the formation of DE in NAA. We found an increase in the concentration of IL-10 and TGF-β1 in patients with NAA. The relationship between anti-inflammatory cytokinemia and indicators of the functional state of the endothelium was revealed. The results of the study showed a higher content of these cytokines in patients with NAA with hypertension III art.

Our studies showed an increase in TGF-β1 in the blood serum of patients with NAA, increasing with the severity of DE and AH. The overproduction of IL-10, TGF-β1, which we established in patients with NAA, is compensatory in response to the activation of inflammation. The pleiotropic properties of TGF-β1 should be noted. If in the early stages of the disease its overproduction is protective and aimed at limiting inflammation, then its persistent overproduction leads to profibrogenic effects, hypertrophy of smooth muscle cells, induces vascular system remodeling processes, thus increasing the risk of cardiovascular complications, which occurs in patients AG against the backdrop of NAA.

We studied the correlation between cellular immunity and the functional state of the circulatory endothelium in patients with NAA, taking into account the role of chronic immune inflammation in the development of endothelial dysfunction in cardiovascular diseases. The data obtained show that in patients with NAA there is a violation of the ratio of the subpopulation composition of peripheral blood lymphocytes compared with the control group . In patients with NAA with stage II hypertension, there is an increase in the number of both CD4 + and CD8 + cells. In the group of patients with NAA with stage III hypertension, there was a tendency to increase the content of CD4 + and CD8 + lymphocytes in comparison with the corresponding parameters in patients with NAA and hypertension stage II. A study of the extracellular immunity revealed an increase in the content of CD20 + lymphocytes in the blood of patients with NAA, which increased with severity of hypertension. An increase in the expression of an early marker of activation of lymphocytes, the alpha chain of the interleukin-2 receptor (CD25 +) and the expression of late activation markers (HLA-DR +) in patients with NAA, is comparable to the stage of hypertension. Assessment of the expression of inducer factor of apoptosis CD95 + on lymphocytes established an increase in CD95 + in patients with NAA, which increased in parallel with the stage of hypertension. Studies have shown exacerbation of cellular immunity disorders in patients with NAA, correlated with the stage of hypertension.

In patients with NAA and AHIII stage, the most pronounced changes in the content of CD4 + (67.7 ± 3.3%), CD8 + (16.6 ± 2.5%) phenotype and an increase in the content of CD20 + (24.3 ± 1.4%) were important .It is also important for them to disturb the expression of early CD25 + (34.3 ± 1.4%), late HLA-DR + (36.1 ± 1.9%) activation markers and inducer apoptosis factor CD95 + (44.8 ± 2.9%). In patients with NAA, the determination of the content of ET-1 with various stages of hypertension revealed an increase in the concentration of ET-1 parallel to the stage of hypertension. In patients with stage III AH, a high level of ET-1 is noted (15.29 ± 1.2 ng / L, $p < 0.01$). The obtained results substantiated the advisability of using medications that have a corrective effect on the immune status and endothelial dysfunction in patients with hypertension with NAA. Clinically promising are examinations of the anti-inflammatory and vasoprotective effects of the main groups of drugs used as pathogenetic therapy for NAA, which will help optimize the treatment of this pathology.

It is known that, despite the relief of signs of activity of systemic vasculitis through pathogenetic therapy of corticosteroids, it is not always possible to improve the prognosis and reduce the risk of developing cardiovascular complications.

According to the literature, it is known that calcium antagonists and ACE inhibitors have a vasoprotective effect, cause regression of vascular remodeling [6; p.92-93], contribute to the correction of endothelial dysfunction, have a beneficial effect on platelet hemostasis and fibrinolysis, increase the formation of NO, reduce the synthesis of endothelin [125; p.342-347]. ACE inhibitors, by reducing the formation of angiotensin II, reduce the activity of macrophage monocytes, inhibit the activation of adhesion molecules and inflammatory mediators, smooth migration omyshechnyh inflammatory cells in the lesion, the growth of smooth muscle cells of the vascular wall [80; s.999-1008,83; s.312]. The preparations of amlodipine and lisinopril determine the ability of the drug to counteract oxidative stress, elimination of reactive oxygen species and other free radicals, that the presence of sulfhydryl group in the structure, initiating the development of immune processes in the vascular wall, the formation of endothelial dysfunction. The equator has an anti-inflammatory and angioprotective effect, which is a fixed combination of an angiotensin-converting enzyme inhibitor lisinopril and a calcium antagonist amlodipine. In the clinical practice of Uzbekistan, an equator drug appeared, consisting of a combination of lisinopril with amlodipine, and in just a few years it took a fairly strong place among modern therapeutic approaches in the treatment of hypertension. The equator drug belongs to the first line of treatment of hypertension, with a good level of evidence regarding the positive effects on the cardiovascular

prognosis. Plavix (clopidogrel) is a modern antiplatelet agent, a representative of the thienopyridine class, it blocks platelet receptors for adenosine diphosphate, reduces their activity and ability to aggregate, and Vitogue reduces the risk of thrombotic complications in various manifestations of stenotic diseases of the aorta and arteries. The study of these mechanisms allows you to control the progression of the disease.

The relevance of this problem lies in the lack of literature data on the impact of calcium antagonists, angiotensin converting enzyme inhibitors and antiplatelet agents on the studied parameters in patients with NAA. Recent studies show the presence of vasoprotective properties in drugs of these groups [22; p. 72-77,124; p. 849- 854].

According to the results of studies in patients with NAA, it is possible to evaluate the effect of antiaggregantaclopidogrel (Plavix) and a fixed combination of calcium antagonist amlodipine and ACE inhibitor lisinopril (Equator) on indicators of immune status, endothelial function and clinical impotatics. We studied 74 patients with NAA, the control group included 30 healthy individuals. All patients were divided into two groups: the first group consisted of 35 patients with NAA, the therapy of which included taking the equator at a dose: lisinopril 10 mg / day, amlodipine 5 mg / day. The second group included patients (39 people) who took the equator at a dose of lisinopril 10 mg / day, amlodipine 5 mg / day and plavix (clopidogrel) 75 mg / day; The duration of treatment with combined drugs was 10 months.

The research results showed a decrease in the level of production of ET-1, endothelial cells during therapy with equator forte in combination with Plavix. This, in turn, leads to a decrease in the regulated ET-1 secretion of catecholamines and other neurohormones (arginine, vasopressin, angiotensin II), which play a leading role in the development and progression of endothelial dysfunction in cardiovascular diseases [40; p. 2009]. combination with plavix was characterized by a significantly more pronounced effect on DE.

Disorders in the hemostasis system are directly related to endothelial dysfunction, since the endothelium is capable of producing many substances that affect platelet and coagulation hemostasis (NO, prostacyclin, thromboxane, surface adhesive molecules, vW, tissue factor, thrombomodulin, tissue plasminogen activator activator, inhibitor plasminogen, surface proteoglycans) [7; p. 67-71]. The effective effect of these drugs on endothelial dysfunction is also confirmed by a significant increase in the percentage of EDVD in groups of patients with NAA after 10 months of therapy. The most pronounced changes in the indicators of the functional state of the endothelium during monotherapy with equator were achieved in patients with NAA with II degree of DE and II stage of hypertension. At the III degree of DE, monotherapy with this drug did not have a significant effect on the studied parameters. The combined use of plavix and equator was accompanied by a significant increase in the vasoprotective effect of therapy, which was manifested by the relief of signs of endothelial dysfunction of the vascular bed in patients with NAA with a II degree of functional distress.

In this disease, taking into account the role of immune disorders in the progression of endothelial dysfunction, a control study of the indicators of immune status and after treatment with the equator and combination therapy equator + Plavix was carried out. In case of NAA with II degree DE with AH stage III, the immune status indicators after a combination of amlodipine with lisinoprilom were different from normal . In patients with NAA with arterial hypertension, stage III, DE II degree, against the background of the use of the equator, correction of immune disorders was achieved. In this disease, the use of anti-inflammatory drugs reduced the activity of the humoral immunity link, correcting cytokine profile disorders in patients with NAA with grade III DE and stopping immune disorders in patients with NAA with signs of grade II DE.

Studies have shown a high degree of correlation between endothelial function and cytokine status in patients with NAA. A direct correlation was determined between the level of ET-1, the content of pro-inflammatory cytokines in the blood serum, the feedback was established between the value of the EDVD and the concentration of these cytokines, which is due to the properties of TNFα, IL-1β, IL-6, IL-8, INF-γ to induce the development and progression of endothelial dysfunction.

Our data indicate the benefits of combined antihypertensive therapy of the equator in conjunction with Plavix. The predominant effect is due not to the mechanical addition of the effectiveness of the drugs prescribed jointly, but to the potentiation of their action, this is due to the fact that drugs of different classes act on different parts of the pathogenesis of NAA, thereby complementing each other's action. The combined use of the equator and plavix allows you to neutralize the activation of counter-regulatory mechanisms that reduce the effectiveness of

drugs. Thus, the combination therapy of calcium antagonists, ACE inhibitors and antiplatelet agents allows you to immediately act on a large number of the most diverse links in the pathogenesis of NAA - activation of RAAS, CAC, endothelial dysfunction, immune inflammation, myocardial and vascular wall hypertrophy, which is why combination therapy solves the problem of multifactoriality of NAA.

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