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EFFECTS OF ANTI-ALLERGIC THERAPY ON BLOOD PRESSURE, SYMPTOMS OF RHINITIS AND LEVEL OF C-REACTIVE PROTEIN IN PATIENTS WITH COMORBID ALLERGIC RHINITIS AND HYPERTENSION

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ABSTRACT

The task of this research was to study the effects of three treatment regimens of anti-allergic therapy on clinical and functional parameters, symptoms of rhinitis, control of blood pressure and systemic inflammation in patients with seasonal allergic rhinitis and essential hypertension.

Totally 73 patients were examined (men – 34 people (46.5%) and women – 39 people (53.5%). All patients were divided into three clinical groups depending on the treatment of seasonal allergic rhinitis. All patients were examined for nasal and non-nasal symptoms of seasonal allergic rhinitis, which was conducted on the total nazal symptom score and total non nazal symptom score 2 times a day (morning and evening), a standardized rhinitis quality of life questionnaire was used to assess the quality of life of patients, blood pressure control was conducted using 24-hour holter monitoring and the level of hs-c-reactive protein was studied. These parameters were studied twice: 3-5 months before the period of pollination (stage 1) and in the period of pollination (stage 2).

In the period of pollination cause-significant allergens in the 2nd and 3rd clinical groups were found the highest total nasal symptom score, total non nasal symptom score, rhinitis quality of life questionnaire, systolic blood pressure, heart rate and C-reactive protein.

The most effective effect on the control of symptoms of seasonal allergic rhinitis, stability of antihypertensive therapy and the level of systemic inflammation was registered in patients who received allergen specific immunotherapy and started therapy with antihistamines one month before pollination of causal allergens.

KEYWORDS: comorbidity, allergic rhinitis, hypertension.

Introduction

More and more attention has been devoted to the peculiarities of diagnosis and treatment of patients with a combination of two or more diseases in recent years [Oganov R et al., 2019].

Kremer HS and Van den Acker M defined the term comorbidity as the coexistence of two and/or more syndromes or diseases in one patient, pathogenetically and genetically interrelated or coincident in time [Vertkin A, 2012].

Diagnosis and management of patients with comorbid pathology remains one of the most difficult

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tasks in real clinical practice for today.

Most patients suffering from cardiovascular diseases (CVD) are characterized by a combination of two or more diseases and conditions, the so-called cardiovascular comorbidity [DuGoff E et al., 2014; Oganov R et al., 2019]. According to the information of Russian outpatient registers, the share of persons with arterial hypertension (AH) among patients who go to polyclinics for CVD is more than 90% [Oganov R et al., 2019]. Poorly controlled hypertension is an important risk factor for CVD, causing about 54% of strokes and 47% of acute coronary events [Lawes C et al., 2008]. The simultaneous presence of high blood pressure and other cardiovascular risk factors can mutually reinforce each other and together give a higher

overall cardiovascular risk [Mancia G et al., 2013].

Due to the geometric increase in the prevalence of allergic diseases in the world, their comorbidity with cardiovascular diseases is of special scientific and practical interest.

From 12.7% to 24% of the population in different regions of the Russian Federation suffer from Allergic rhinitis (AR). AR occurs in all age groups and is often combined with Hypertension (AH) [Beltyukov E, Bratukhin K, 2015]. Persistent inflammatory process is an important pathogenetic link as an independent risk factor in AH, and as a pathogenetic characteristic of inflammation in AR [Corbo G et al., 2006]. Exacerbation of chronic persistent inflammation during pollination of a causally significant allergen in seasonal AR can potentially affect systemic subclinical low-intensity inflammation, which plays an important role in the pathogenesis of CVD [Savoia C, Schiffrin E, 2007]. The association of increasing the concentration of markers of systemic inflammation C-reactive protein (CRP) with the development of complications of CVD was proved [Milutina O, Chicherina E, 2011]. Several research studies suggested that CRP is an active participant in the development of not only immuno-inflammatory reactions, but also atherosclerosis [Milutina O, Chicherina E, 2011; Hong Seog Seo, 2012].

During previous research studies, we have shown that pollination of causally significant allergen in patients with seasonal AR (SAR) and AH lead to "eluding" the effect of antihypertensive therapy, increasing the level of CRP in the framework of lowintensity inflammation [Usachenko Y, Beloglazov V, 2018]. Taking into account, the study of the influence of therapeutic strategies for the treatment of AR on the course of comorbid hypertension is of absolute scientific and practical interest.

The task of this research was to study the effects of three treatment regimens of anti-allergic therapy on clinical and functional parameters, symptoms of rhinitis, control of blood pressure and systemic inflammation in patients with seasonal allergic rhinitis and essential hypertension.

MATERIALS AND METHODS

Totally 73 patients were examined (men – 34 people (46.5%) and women – 39 people (53.5%)) living in the Republic of Crimea. The criterion for inclusion in the study was the presence of comorbid pathology in patients: SAR and essential AH of 1-2 degrees. The age of patients was 45.7±1.1 years. All patients were divided into three clinical groups depending on the treatment of SAR. Group 1 - 21 patients after a course of pre - season allergen specific immunotherapy (ASIT), which they received during the period of remission of SAR; group 2 – 23 patients who started receiving antihistamines (desloratadine 5 mg/day) a month before the start of the period of pollination of causally significant allergens and the appearance of symptoms of rhinitis; and group 3-29 patients who used antihistamines (desloratadine 5 mg/day) for the relief of already developed symptoms of SAR, as well as vasoconstrictive nose drops (Oxymetazoline Hydrochloride) and eye drops (cromoglycic acid solution). All patients received antihypertensive therapy (angiotensin converting enzyme (ACE) inhibitors and beta-blockers). Assessment of the severity of SAR symptoms during pollination of causally significant allergens was determined on the basis of Aria recommendations (WHO, 2010) [Brożek J et al., 2017]. Essential hypertension was diagnosed according to the criteria of the European and Russian society of cardiology [Mancia G et al., 2013].

The study did not include patients with secondary hypertension, malignant hypertension, with the presence of acute inflammatory processes and

chronic in the acute stage, diabetes, thyroid diseases (hypothyroidism and hyperthyroidism), renal and hepatic pathology, hematological diseases, cancer, alcoholism, drug addiction, connective tissue diseases, diseases of the central and peripheral nervous system, mental diseases, chronic heart fail-

> To overcome it is possible, due to the uniting the knowledge and

ure 3rd-4th functional classes by the New York Heart Association and the presence of hemodynamically significant heart defects.

The control group consisted of 20 practically healthy individuals without SAR and essential AH comparable in age and sex, were examined once.

The study of blood pressure (BP) was carried out with the help of 24-hour Holter blood pressure monitoring with the use of cardioregistrator "Dia-Card". BP monitoring was performed within 24 hours. During the study, patients followed a normal daily order and noted in a diary changes in health throughout the study. During the daily monitoring of BP, the following indicators were calculated: average heart rate, average systolic blood pressure (SBP) and diastolic blood pressure (DBP) during the day.

The level of hs-C-reactive protein (hs-CRP) in the blood serum of patients was determined by quantitative highly sensitive enzyme immunoassay with the use of ELISA test, the results were expressed in mg/l.

The study also assessed the effectiveness and impact on the quality of life of patients with comorbidity of SAR and AH three therapy regimens. The effectiveness criteria were the evaluation of the effect of three regimens of therapy on nasal (nasal congestion, rhinorrhea, itching in the nose, sneezing) and abnormal (itching and/or burning sensation in the eye area, watery eyes, red eyes, itching in the ears or palate) symptoms of SAR, which was conducted on the scales TNSS (Total Nasal Symptom Score) and TNNSS (Total Non-Nasal Symptom Score). Rhinitis symptoms were evaluated 2 times a day (morning and evening) on a scale (0-3 points):

- 0 absence of symptoms;
- 1-symptoms present but easily tolerated, disturb minimally;
- 2-symptoms are clearly disturbing, not tolerable
- 3-symptoms are expressed significantly, worsen the quality of life and endured with difficulty.

The standardized quality of life questionnaire RQLQ (Rhinitis Quality of Life Questionnaire) was used to assess the quality of life of patients with seasonal AR and AH.

These parameters were studied twice: 3-5

months before the period of pollination (stage 1) and in the period of pollination (stage 2).

Statistical analysis of the material was carried out using Microsoft Office Excel 2007 and Statistica 10.0 (StatSoft). The studied parameters are presented as a median (Me) indicating the 25th and 75th percentiles of their distribution. To compare quantitative data, nonparametric methods were used – the Mann-Whitney test (Mann-Whitney Utest) for two independent samples and the Wilcoxon test (Wilcoxon matched pairs test) for comparing two dependent samples. The differences were regarded as statistically significant at the achieved level of significance p<0.05.

RESULTS

The results of the study of the dynamics of the average daily monitoring of BP and heart rate in these groups of patients with comorbid pathology, depending on the treatment received, are presented in table 1.

As follows from the data presented in table 1 in the period of pollination of causally significant allergens, an increase in the average daily SBP according to monitoring BP was recorded in the group of patients with comorbid course of SAR and AH. The most significant increase in the average daily SBP was registered at the 2nd stage of the study in the 3rd group of patients receiving symptomatic therapy SAR – 147 [133; 156.5] mm Hg was found that significantly higher indicators in the comparative analysis of groups 1 and 2-persons who received ASIT before the beginning of the period of pollination of causally significant allergens and antihistamines for month before the beginning of the period of pollination, where p=0.007 and p=0.012. It is also worth noting that the average daily SBP in patients of the 1st and 2nd groups had no significant differences, p=0.278. A comparative analysis of the average daily SBP in the groups between the 1st and 2nd stage revealed a significant increase in data in the period of exacerbation in all groups.

The analysis of the average daily DBP between the groups revealed a significant increase in indicators at the 2nd stage of the study in patients of the 3rd group – 89 [77.5; 97] *mm Hg* patients with symptomatic treatment of SAR in comparison with the 1st and

Table 1

Effect of treatment of seasonal allergic rhinitis on the level of daily monitoring of blood pressure and heart rate in persons with comorbid pathology of seasonal allergic rhinitis and hypertension

Parameter		Stage	Group 1 Group 2 Group 3 Stage Me $[Q_{25}; Q_{75}]$ Me $[Q_{25}; Q_{75}]$ Me $[Q_{25}; Q_{75}]$ n=29		Group 4 (Control) Me [Q ₂₅ ; Q ₇₅] n=20			
systolic blood	pressure for days, $mm\ Hg$	1	130 [126; 134]	129 [128; 134]	136 [128; 139]	124.5 [119; 126.5]	$\begin{array}{l} p_{(1\text{-}4)} < 0.001 \\ p_{(3\text{-}4)} < 0.001 \\ p_{(1\text{-}3)} = 0.947 \\ p_{(1\text{-}1)} = 0.032 ** \\ p_{(3\text{-}3)} < 0.001 ** \end{array}$	$\begin{array}{c} p_{(2\text{-}4)} < 0.001 \\ p_{(1\text{-}2)} = 0.723 \\ p_{(2\text{-}3)} = 0.916 \\ p_{(2\text{-}2)} < 0.001 ** \end{array}$
Average		2	137 [130; 145]	138 [136; 145]	147 [133; 156.5]		$\begin{array}{c} p_{(1\text{-}4)} < 0.001 \\ p_{(3\text{-}4)} < 0.001 \\ p_{(1\text{-}3)} = 0.007 * \end{array}$	$\begin{array}{c} p_{(2\text{-}4)} = 0.046 \\ p_{(1\text{-}2)} = 0.278 \\ p_{(2\text{-}3)} = 0.012 * \end{array}$
Average diastolic	blood pressure for days, $mm\ Hg$	1	77 [73; 87]	75 [68; 79]	78.5 [71; 89]	70 [68; 74.5]	$\begin{array}{l} p_{_{(1\text{-}4)}}\!\!<\!\!0.001\\ p_{_{(3\text{-}4)}}\!\!=\!\!0.073\\ p_{_{(1\text{-}3)}}\!\!=\!\!0.556\\ p_{_{(1\text{-}1)}}\!\!=\!\!0.179\\ p_{_{(3\text{-}3)}}\!\!=\!\!0.005\!** \end{array}$	$\begin{array}{l} p_{_{(2\text{-}4)}}\!\!<\!\!0.001\\ p_{_{(1\text{-}2)}}\!\!=\!\!0.768\\ p_{_{(2\text{-}3)}}\!\!=\!\!0.655\\ p_{_{(2\text{-}2)}}\!\!=\!\!0.286 \end{array}$
Avera		2	84 [76; 95]	76 [72; 83]	89 [77.5; 97]		$\begin{array}{c} p_{(1\text{-}4)} < 0.001 \\ p_{(3\text{-}4)} < 0.001 \\ p_{(1\text{-}3)} = 0.015 * \end{array}$	$\begin{array}{c} p_{(2\text{-}4)} = 0.002 \\ p_{(1\text{-}2)} = 0.287 \\ p_{(2\text{-}3)} < 0.001 * \end{array}$
Average heart rate	during the day, heartbeats per min.	1	67 [55; 71]	69 [62; 72]	78 [72; 80]	70 [64.5; 77.5]	$\begin{array}{l} p_{(1\text{-}4)}\!\!<\!\!0.001 \\ p_{(3\text{-}4)}\!\!<\!\!0.001 \\ p_{(1\text{-}3)}\!\!=\!\!0.021^* \\ p_{(1\text{-}1)}\!\!<\!\!0.001^{**} \\ p_{(3\text{-}3)}\!\!<\!\!0.001^{**} \end{array}$	$\begin{array}{l} p_{_{(2\text{-}4)}}\!\!<\!\!0.001\\ p_{_{(1\text{-}2)}}\!\!=\!\!0.934\\ p_{_{(2\text{-}3)}}\!\!=\!\!0.098\\ p_{_{(2\text{-}2)}}\!\!<\!\!0.001** \end{array}$
Averag		2	82 [75; 90]	80 [71; 106]	89 [84; 92]		$\begin{array}{c} p_{(1\text{-}4)} < 0.001 \\ p_{(3\text{-}4)} < 0.001 \\ p_{(1\text{-}3)} = 0.066 \end{array}$	$\begin{array}{c} p_{(2-4)} < 0.001 \\ p_{(1-2)} = 0.375 \\ p_{(2-3)} = 0.076 \end{array}$

Notes: p – significant differences at p<0.05 with the control group, according to the Mann-Whitney U-test; *p – significant differences at p<0.05 between groups, according to the Mann-Whitney U-test; **p – significant differences in p<0.05 one group between 1 and 2 stages of the study, according to the T- Wilcoxon test.

2nd group of patients receiving ASIT and antihistamine therapy for month before the onset of exacerbation of symptoms of SAR, respectively, p=0.015 and p=0.001. A comparative analysis of the average daily DBP in the groups between the 1st and 2nd stage revealed a significant increase in data in the period of exacerbation only in the 3rd group, p=0.005.

The level of heart rate in all groups of patients was significantly higher compared to the control group at the 1st and 2nd stage of the study. In the comparative analysis between the groups, a significant increase in the average daily heart rate was recorded only by the 1st and 3rd groups at the 1st stage of the study, p=0.021. A comparative analysis of the average daily heart rate in the groups between the 1st

and 2nd stage revealed a significant increase in data in the period of exacerbation in all groups, p<0.001.

Before treatment, all patients had the same severity of SAR symptoms. As a result of the treatment, patients demonstrated a clinical improvement in the symptoms of SAR presented in table 2. The best clinical effect was found in the 1st and 2nd groups of patients, who received as therapy ASIT in remission of SAR and antihistamines month before the beginning of the period of pollination of causal allergens. A comparative analysis between the groups revealed a significant difference between the 1st and 3rd group and the 2nd and 3rd group, respectively, for the scale TNSS p<0.001 and p<0.001 and TNNSS p<0.001 and p<0.001. There were no significant difference difference between the 1st and 3rd group and the 2nd and 3rd group, respectively, for the scale TNSS p<0.001. There were no significant difference between the 1st and 3rd group and the 2nd and 3rd group, respectively, for the scale TNSS p<0.001. There were no significant difference between the 1st and 3rd group and the 2nd and 3rd group and TNNSS p<0.001 and p<0.001. There were no significant difference between the 1st and 3rd group and the 2nd and 3rd group and TNNSS p<0.001 and p<0.001. There were no significant difference between the 1st and 3rd group and the 2nd and 3rd group and TNNSS p<0.001 and p<0.001.

TABLE 2
Effect of the treatment of seasonal allergic rhinitis on nasal and nonnasal symptoms, as well as on quality of life in persons with comorbid
pathology of seasonal allergic rhinitis and hypertension

Parameter		Group 2 Me [Q ₂₅ ; Q ₇₅] n=23		Significance of differences
TNSS	1.25	1.50	2.00	$\begin{array}{c} p_{(1-2)} = 0.339 \\ p_{(1-3)} < 0.001* \\ p_{(2-3)} < 0.001* \end{array}$
(mark)	[1.00;1.63]	[1.38;1.75]	[1.75;2.13]	
TNNSS	1.50	1.75	2.43	$ \begin{vmatrix} p_{(1-2)} = 0.055 \\ p_{(1-3)} < 0.001* \\ p_{(2-3)} = 0.001* \end{vmatrix} $
(mark)	[1.00;1.75]	[1.50;2.00]	[2.00;2.75]	
RQLQ	40.0	42.0	47.0	$\begin{array}{c} p_{(1-2)} = 0.741 \\ p_{(1-3)} = 0.011* \\ p_{(2-3)} = 0.029* \end{array}$
(mark)	[37.0;47.0]	[33.0;47.0]	[41.0;53.0]	

Note: *p - significant differences at p < 0.05 with the control group, according to the Mann-Whitney U-test.

ferences between TNSS and TNNSS in the comparative analysis of the 1st and 2nd groups.

The analysis of the questionnaire RQLQ revealed a significant difference between the 1st and 3rd group, p=0.011 and the 2nd and 3rd group, p=0.029. The data presented in the 1st and 2nd groups do not differ statistically, which indicates an improvement in the quality of life in patients of both groups.

Analyzing the data presented in table 3, it was found that the level of hs-CRP in all groups of patients was significantly higher compared to the control group at the 1st and 2nd stage of the study. In the period of remission of symptoms of SAR between the groups the significant differences were

not registered, but in the period of exacerbation of SAR revealed a significant difference between the 1st and 3rd groups, p=0.015 and the 2nd and 3rd groups, where p=0.006. It should be noted that the revealed fact of the highest increase in the concentration of hs-CRP in the blood of patients of group 3 during the pollination of causally significant allergens -6.0 [5.0; 6.9] mg/l, they received symptomatic therapy with SAR, which is significantly higher than in group 2 - 2.9 [1.9; 5.0] mg/l, p=0.006. There was also a significant difference between the 1st and 2nd stage in patients of groups 2 and 3, p=0.016 and p<0.001. The level of hs-CRP in

the 2nd period is included in the zone of so-called systemic inflammation of low intensity.

DISCUSSION

Allergic diseases is a systemic inflammatory condition that can potentiate CVD [Corbo G et al., 2006; Savoia C, Schiffrin E, 2007; Milutina O, Chicherina E, 2011; Hong Seog Seo, 2012]. Information about the negative impact of allergies on levels BP contained in the study S. Kony and coauthors (2003), in which, it was shown that in men with seasonal and chronic rhinitis by an average of 3.5 mm hg. art. SBP is higher than in patients without allergic rhinitis [Kony S et al., 2003].

Table 3

Effect of the treatment of seasonal allergic rhinitis on the level of C-reactive protein in persons with comorbid pathology of seasonal allergic rhinitis and hypertension

Parameter	Stage	Group 1 Me $[Q_{25}; Q_{75}]$ $n=21$	Group 2 Me $[Q_{25}; Q_{75}]$ $n=23$	Group 3 Me [Q ₂₅ ; Q ₇₅] n=29	Group 4 (Control) Me [Q ₂₅ ; Q ₇₅] n=20	Significance of differences	
CRP mg/l	1	2.2 [1.4; 4.2]	2.0 [1.5; 2.5]	2.4 [1.9; 2.5]	0.56 [0.3; 0.9]	$\begin{array}{c} p_{(1\text{-}4)<0}.001 \\ p_{(3\text{-}4)}<0.001 \\ p_{(1\text{-}3)}=0.982 \\ p_{(1\text{-}1)}=0.078 \\ p_{(3\text{-}3)}<0.001** \end{array}$	$\begin{array}{c} p_{(2\text{-}4)} \!\!<\!\! 0.001 \\ p_{(1\text{-}2)} \!\!=\!\! 0.528 \\ p_{(2\text{-}3)} \!\!=\!\! 0.512 \\ p_{(2\text{-}2)} \!\!=\!\! 0.016 \!\!*\!\!* \end{array}$
8/1	2	3.0 [2.2; 5.2]	2.9 [1.9; 5.0]	6.0 [5.0; 6.9]		$\begin{array}{c} p_{(1\text{-}4)} < 0.001 \\ p_{(3\text{-}4)} < 0.001 \\ p_{(1\text{-}3)} = 0.015 * \end{array}$	$\begin{array}{c} p_{(2\text{-}4)} < 0.001 \\ p_{(1\text{-}2)} = 0.764 \\ p_{(2\text{-}3)} = 0.006* \end{array}$

As follows from the results of the research – treatment of SAR with ASIT or antihistamines before the onset of symptoms of rhinitis prevents the level of SBP, both during exacerbation and during remission of SAR. Also, the above treatment regimens can control nasal and non-nasal symptoms of SAR and improve the quality of life of patients with comorbidity of SAR and AH.

From the data obtained by us, it should be concluded that the level of CRP increase to the range of low-intensity inflammation in patients with SAR and AH only in the group of patients used antihistamines medicines only in the period of pollination of a causally significant allergen.

As you know, CRP is an active participant in the development of not only inflammatory reactions but also of atherosclerosis [Milutina O, Chicherina E, 2011; Hong Seog Seo, 2012], as well as the central protein of acute phase of inflammation can increase inflammatory cascade, inducing the production of proinflammatory cytokines, primarily interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) in peripheral mononuclear cells and alveolar macrophages [Eizadi M et al., 2011], activating the complement system, stimulating low density lipoproteins (LDL) uptake by macrophages and increasing the leukocyte adhesion to the vascular endothelium [Verma S et al., 2002]. It is proved that even with low allergen concentration and absence of symptoms, so-called minimal persistent inflammation persists in patients with AR [Trushchenko NV, 2014].

As our studies have shown, the pre-season program of ASIT and antihistamine therapy month before the onset of symptoms of AR does not allow to increase the level of CRP to the level of low-intensity systemic inflammation, thus reducing its role as a risk factor for cardiovascular events, and also leads to more effective control the symptoms of rhinitis, as well as improve the quality of life in the comorbid patient. This fact is associated with the pleiotropic effect of antihistamines (membrane stabilizing and anti-inflammatory effect) in this scheme of their prescription. While the appointment of antihistamines only in the period of exacerbation of SAR, this effect does not have time to

develop. Therefore, the prescription of therapy controlling the symptoms of rhinitis potentially reduces the development of inflammation of the respiratory tract.

Thus, the purpose of primary care for AR is to suppress allergic inflammation and hypersensitivity of the nasal mucosa, which are enhanced by repeated exposure to even a small amount of allergen [Kimihiro O et al., 2014].

In order to improve the quality of life of patients, it is necessary to use ASIT and early prescription of antihistamines in SAR, which allows to improve the control of symptoms of rhinitis and hypertension, as well as to reduce the role of systemic inflammation in the comorbid course of hypertension and SAR.

With the aim of improving the quality of life of patients with SAR, it is necessary to use ASIT or early prescription of antihistamines 2nd generation, which allows to improve the control of symptoms of rhinitis and hypertension, as well as to reduce the influence of low-intensity systemic inflammation as an independent risk factor of cardiovascular events in comorbid for AH and SAR.

Conclusion

The most effective effect on the control of AR symptoms, maintaining the stability and effectiveness of background antihypertensive therapy and the level of systemic inflammation was registered in patients who received ASIT in the 1st clinical group and began therapy with antihistamines 1 month before pollination of causally significant allergens in the 2nd clinical group.

The least effective effect on the studied indicators of control of symptoms of SAR, AH and systemic inflammation was the use of antihistamines only in exacerbation of SAR.

In persons with comorbid course of SAR and AH more extensive use of preseason ASIT or the prescribe of antihistamines a month before pollination of causal significant allergens for improve the control of nasal and non-nasal symptoms of rhinitis, maintain the stability of background AH and prevent increase systemic inflammation is recommended.

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