The State of Immune Reactivity During the Treatment of Genital Herpes in Patients Who Have Undergone Covid-19

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Abstract

Relevance: Relapses of herpes simplex during the COVID-19 pandemic in patients with or without respiratory symptoms alarm us about the possibility of SARS-CoV-2 infection in these patients.

Both the stress caused during the pandemic and the invasion of SARS-CoV-2 itself are generative elements of immunodeficiency in humans, a situation that can be used by the herpes virus to reactivate and infect the host (1).

Keywords: SARS-CoV-2, Recurrent Genital Herpes, HSV-1, HSV-2.

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INTRODUCTION

Genital herpes is a lifelong sexually transmitted infection caused by herpes simplex virus type 2 herpes simplex virus (HSV-2) and type 1 (HSV-1), and is characterized by recurrent, self-canceling outbreaks of painful lesions of the genitals in some infected (2). It should be noted that currently the leading criterion underlying the determination of the management tactics of a patient with herpes simplex (HS), an assessment of the severity of the disease, has been missed. However, regardless of the location of the rash, the severity of immune disorders and the possible negative consequences of HSV are the same and require a unified approach depending on the frequency of relapses. It is the frequency of exacerbations that determines the severity of HS that should underlie the therapeutic approach (3). It is worth noting that due to the ability of the herpes simplex virus to persist for a long time, leading to a decrease in antiviral immune protection, the treatment of patients with herpes simplex is a complex problem (4).It should also be taken into account that the loss of control of the immune system over the latent state of HSV in the paravertebral ganglia occurs with a decrease in the interferon system, which plays an important role in the mechanisms controlling the latent state of chronically persistent viral infections (5).

It is known that none of the currently existing drugs are able to eliminate the virus from the body. Therefore, in the treatment of genital herpes, correction of immune defense mechanisms by the use of targeted immunomodulators becomes important.

Immunomodulatory drugs can delay the elimination of the virus when administered prematurely, and can also affect the course of tissue repair (6).

Another promising substance with antiviral activity against HSV is glycyrrhizin. Previously reported anti-inflammatory and immunoregulatory properties of glycyrrhizin (7) Glycyrrhizin inhibits the penetration of HSV-1 into cells by targeting adhesion molecules on the surface of target cells (8).

Objective: To study immune reactivity in patients with recurrent genital herpes (RGH) who have undergone

COVID-19 in the course of the complex therapy developed by us with acyclovir, glycyrrhizin and the interferon inducer gozalidone. An important property of interferons is the ability to interfere with intracellular replication of viruses by activating the cell's response to viral infection. IFN triggers a cascade of biochemical reactions in cells that lead to the suppression of the synthesis of viral proteins.

Materials and Methods

Under our supervision there were 66 patients with RGH who had suffered COVID-19, aged 18 to 50 years, including 24 men and 42 women. The duration of the disease varied from 1 year to 9 years. There were 24 patients with mild RGH (relapses 1-3 times a year), with moderate -23 (relapses 4-6 times a year), with severe – 19 (relapses more than 6 times a year) people. All patients were examined for sexually transmitted infections, and antibody titers to SARS-CoV-2 were determined in the Enzyme Immunoassay (EIA) test. The diagnosis was carried out on the basis of the clinical picture of the disease and laboratory data (PCR test, as well as Enzyme Immunoassay (EIA) with the determination of antibodies to HSV -1 and HSV-2). Wasserman's reaction was negative in all cases. The immune parameters were evaluated using monoclonal antibodies produced by the Institute of Immunology of the Ministry of Health of the Russian Federation (Moscow).

According to the method of treatment used, the patients were divided into 2 similar groups. The first group of patients (34) received traditional treatment, including episodic therapy: acyclovir, 200 mg orally 5 times a day for 7 days, vitamins C, E, group B, externally aniline dyes, acyclovir, cream 3%; preventive therapy for moderate and severe forms of RGH: acyclovir, 400 mg orally 2 times a day for up to 3-4 months. Patients of the second group (32) received combined pathogenetic therapy with acyclovir, glycyrrhizin solution, 20 ml intravenously for 10 days and gozalidone 0.1 g orally 2 times a day in 2 cycles of 3 days with an interval of 3 days, externally megosin, ointment 3% (episodic therapy); and as a preventive treatment – gozalidone, 0.1 g inside 2 times a day for 3 days with 3-day intervals for 4 -10 cycles, depending on the severity of the course.

The effectiveness of treatment was assessed by reducing the duration of relapse, increasing the duration of remission, as well as by indicators of immune status. The treatment was considered effective with significant improvement and improvement. The patients were followed up for 6-12 months.

Results and Discussion

Studies have shown that patients with RGH were characterized by changes in the immune status, defined as secondary immunological insufficiency (SII), caused, in particular, by disorders in the cellular link. Decreases in relative and absolute CD3+; CD4+, CD4+/CD8+ index, and phagocytic function of neutrophils indicated a general inhibition of immunological protection inherent in patients suffering from chronically recurrent viral infection of the genitals. At the same time, the severity of SII in patients with different clinical forms of RGH was not the same. So, if, according to the analysis of individual and average group values of immunograms, violations in the immune status in patients with mild RGH were transient in nature, then in patients with more frequent relapses of RGH they acquired a persistent character.

The analysis of the obtained immunograms of patients with RGH after the applied treatment methods showed the following (Table). The average relative values of CD3+ lymphocytes after treatment with complex therapy increased relative to the baseline values, and, with a mild form of RGH, they approached the control values ($P>0.05$).

In patients treated with traditional therapy, the level of CD3+ cells it did not differ from those of the initial ones in the moderate form and was lower than the initial indicators in patients with mild and severe forms of RGH ($P<0.05$).

Table: Indicators of immunograms of patients with RGH who underwent COVID-19, treated with various methods

Indicators	Practically healthy n=15	Light form		Medium severe form		Severe form	
		Exodus n=16	Complex method / Traditional.method n=12/12	Exodus n=15	Complex method / Traditional.method n=11/12	Exodusn=15	Complex method / Traditional.method n=9/10
CD3+,%	62,1 ± 2,8	57,3± 2,3	59,1±1,4 51,0±1,5***	43,6± 2,5	50,2±3,1*** 45,9±2,2*	37,0± 1,4	45,1±2,4*** 33,3±1,7***
Cl /mCl	1583 ± 126	1650± 94	1382±56** 1403±90**	1347±133	1214±162* 1101±106*	1053± 74	1077±83* 850±71***
CD4+,%	30,1 ± 2,1	27,0± 1,2	32,1±2,2** 24,2±1,5***	23,7± 1,4	27,3±1,6** 24,5±1,7*	18,6± 0,8	27,7±1,6** 20,9±1,1***
Cl /mCl	486 ± 58	446 ± 31	449±41 329±25***	323 ± 40	327±35* 256±17*	194 ± 16	301±30*** 176±16*
CD8+,%	15,8 ± 0,8	16,4± 0,7	15,6±0,9 14,0±0,7***	16,6 ± 0,8	15,1±0,8 16,0±0,9	15,0± 0,7	14,0±0,7 15,6±1,0
Cl /mCl	248 ± 24	264 ± 18	219±19** 199±20***	223 ± 26	184±20* 170±14****	156 ± 13	151±14* 133±15*
CD4+/ CD8+	1,90 ± 0,07	1,67± 0,1	2,0±0,7** 1,75±0,1*	1,46 ± 0,1	1,8±0,1** 1,5±0,1	1,24 ±0,09	1,92±0,1 1,59±0,2*
CD22+	12,13 ± 1,2	17,6± 0,5*	11,5±0,4** 15,5±0,4***	22,8 ± 2,0	16,0±1,5*** 18,4±0,8***	24,6± 0,5	14,7±0,8** 18,0±1,2***
Cl /mCl	306 ± 35	509 ± 25	318±7** 427±27***	694 ± 70	375±33** 434±32**	691 ± 33	355±34** 461±45***
CIC, circulating immune complex	11,03± 0,65	16,4± 0,7	13,2±0,4*** 13,6±0,7***	23,1 ± 1,2	16,0±1,4*** 18,4±0,8***	24,8± 0,8	17,1±0,9*** 23,1±1,2*
Percentage of phagocytosis	54 ± 2,8	49,8± 2,2	56,0±2,3 50,9±1,7	44 ± 1,9	50,1±2,5** 46,5±2,1*	38,9± 1,2	44,0±1,8*** 34,3±1,8

Note: the indicators statistically significantly different from the control data (healthy) are marked with one *, from the initial data with two **, $P \leq 0.05$. In the numerator – data after treatment with complex therapy, in the denominator – after traditional therapy.

The absolute number of CD3+ lymphocytes during therapy with both methods in patients with mild form became lower relative to the baseline and approached the control indicators. In patients with moderate and especially severe forms of RGH who received traditional therapy, the absolute values of these cells were subjected to even greater suppression than in those treated with complex therapy. The relative values of CD4 lymphocytes underwent significant recovery in all patients with RGH receiving complex therapy. Conventional therapy had no significant effect on this population of lymphoid cells.

The absolute values of CD4+ cells practically did not differ from the initial values in patients with mild and moderate forms of RGH treated with complex therapy, whereas in patients with severe form, when using this therapy, they were statistically significantly higher than the initial values ($P<0.05$). There were no significant shifts in the relative indicators of CD8+ lymphocytes with the use of both types of therapy.

Only in patients with a mild form of RGH who received traditional therapy, these indicators were statistically significantly inhibited in relation to the baseline and control data in healthy patients ($P<0.05$). Similar dynamics was observed with respect to the absolute values of CD8+ lymphocytes. The ratios of CD4+/CD8+ cells in all patients with RGH receiving complex therapy increased, and statistically significantly from the initial values ($P<0.05$), and approached the indicators of practically healthy individuals. At the same time, when using traditional therapy, the immunoregulatory index was significantly lower than the control indicators. Both types of therapy helped to restore the values of CD 22+ cells. At the same

time, the correction of their indicators in all patients with RGH to a pronounced extent occurred with the use of complex immunomodulatory therapy.

The concentration of circulating immune complexes (CIC), initially elevated in patients with all clinical forms of RGH, was significantly inhibited and corrected, especially in patients with moderate and severe forms, and most pronounced when using complex therapy. Positive changes were noted after treatment and in the indicators of the absorption function of neutrophils. At the same time, the percentage of phagocytosis activity in all patients with RGH increased significantly with the use of combined therapy with glycirizzin and gozalidone, rather than with traditional therapy. The absolute phagocytic index in patients treated with traditional therapy remained at a level below the baseline and those of patients receiving complex therapy.

Thus, in all patients with RGH who underwent COVID-19, traditional therapy did not have a pronounced effect on immunological parameters. The use of complex pathogenetic therapy contributed to a significant positive dynamics of the immune system indicators in patients with mild RGH. In patients with moderate and, in particular, with severe forms of RGH, the use of glycyrrhiz and gozalidone against the background of etiotropic therapy had a pronounced corrective effect on the activity of individual immunocompetent cells, possibly due to the manifestation of synergism of their action and increased immunomodulation.

Conclusion

As observations have shown, the use of the interferon inducer gozalidone and glycyrrin, both as part of episodic and as part of long-term preventive therapy in patients with RGH who underwent COVID-19, undoubtedly affected both the manifestations of the frequency and severity of relapses, and the quality of life of patients in general. The duration of relapses and duration of remission after the applied types of therapy were taken into account when assessing the clinical efficacy in patients with RGH. The best results were observed in patients treated with complex therapy, where the average relapse period decreased by an average of 4.4; 2.9 and 3.5 days, respectively, according to the severity of the course of RGH. At the same time, the relapse in these patients was milder, the strength and intensity of subjective symptoms decreased faster, and the general phenomena were also less pronounced. Long-term results indicated a pronounced prolongation of the inter-relapse period in patients receiving episodic and preventive therapy with gozalidone and glycyrrhizin than in patients treated with traditional therapy. So, if, after traditional therapy with mild, moderate and severe forms of RGH, the duration of this period increased by 1.25; 1.26 and 1.47 times, respectively, then in patients on complex therapy it increased by 1.85; 2.29 and 2.97 times, respectively, with mild, moderate and severe forms of the course of RGH.

Thus, the long-term results of the therapy of RGH in patients who have undergone COVID-19 show high efficacy of combined etiotropic therapy with acyclovir with the immunomodulator glycyrrhizin and the interferon inducer gozalidone.

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