PATIENTS WITH PEMPHIGUS VULGARIS UNDER PATHOLOGY AND ON THE BACKGROUND OF PROLONGED USE OF HIGH DOSES OF GLUCOCORTICOSTEROID THERAPY – THE POSSIBILITY OF INFLUENCING THE GLUTATHIONE SYSTEM

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Abstract

Introduction. Pemphigus vulgaris (PV) is a life-threatening disease of the skin and mucous membranes that is associated with IgG antibodies that target several types of keratinocyte antigens and cause epidermal lysis (acantholysis) via intracellular signaling that activates apoptotic enzymes (apoptolysis).

The aim of the study was to increase the effectiveness of treatment of patients with PV with the substantiation and development of modern methods of corrective therapy based on the study of indicators of changes in the balance of the thiol-disulfide system in the body of patients under pathological conditions and with prolonged use of high doses of glucocorticosteroid hormones (GCS).

Materials and research methods. There were examined 30 patients with PV (4 men and 26 women), who were hospitalized in KU «Zaporizhzhya Regional Skin and Venereal

Clinical Dispensary» ZOR, Zaporizhzhia. At the time of observation, most of the patients were aged 61-70 years. As a comparison group, 20 practically healthy people were examined, constituting a control group.

Our studies were four-phase: before treatment; 2-3 weeks of maximum doses of glucocorticosteroids (stage I); 1.5-2 months before discharge from the hospital, when the patient was gradually reduced dose of systemic glucocorticosteroids and the selection of the optimal daily dose (stage II); after 5-6 months, when doses of hormones were minimal (2-3 tablets) in the absence of clinical manifestations of vesicles (stage III).

Results. Our pathogenetic therapy by GCS significantly led to an increase in the level of reduced glutathione (GSH), so in particular after the third treatment stage it was at 1.52 ± 0.13 mkm / mg protein, exceeding the same rate of the first and second stages of GCS administration by 87.65 and 61.70%, respectively ($p < 0.05$). The course of GCS therapy in patients with PV contributed to the fact that the level of reduced thiols increased significantly during each stage of therapy of the examined patients, in particular in the third stage of maintenance GCS therapy reduced thiols were determined at 15.64 ± 1.23 mM / mg protein, exceeding this marker of the second stage by 36.95%, and the value of reduced thiols of the first stage by 83.78% ($p < 0.05$). The value of reduced thiols of the group of patients with PV in the second stage was 11.42 ± 1.08 mM / mg protein, and in the first stage – 8.51 ± 0.92 mM / mg protein, the percentage difference between these therapeutic stages was determined in 34.19% ($p < 0.05$).

Prescribing systemic GCS to patients with PV for three stages led to the restoration of the balance of the thiol-disulfide system in patients, which manifested itself in the form of a decrease in markers: oxidized glutathione and oxidized thiols; and also in the form of an increase in the level of markers of restorative processes – glutathione reductase, glutathione peroxidase, reduced glutathione, reduced thiols, exerting a systemic positive effect on the course of the pathological process, which was reflected both in the normalization of laboratory parameters in patients and clinically in the form of stable remission.

Conclusion. GCS therapy helps to normalize the activity of the antioxidant system of the human body under conditions of PV pathology, which prevents deprivation of the glutathione chain of the thiol-disulfide system during activation of oxidative and nitrosative stress processes and prevents the development of decompensation of the antioxidant system as a whole with the development of damage to key cells and target organs.

Key words: pemphigus vulgaris; glucocorticosteroids; glutathione reductase; glutathione peroxidase; thiols.

Introduction. Pemphigus vulgaris (PV) is a life-threatening disease of the skin and mucous membranes that is associated with IgG antibodies that target several types of keratinocyte antigens and cause epidermal lysis (acantholysis) via intracellular signaling that activates apoptotic enzymes (apoptolysis). The incidence of PV is a total of 0.5-3.2 cases per 100 thousand population [1].

The etiological factors of the pathological autoimmune reaction in PV are multiple and diverse, and the last common stage in this process is the loss of normal immune autotolerance in the stratified squamous epithelium. Analysis of genetic factors influencing the development of PV showed that the same genetic loci can contribute to the development of different forms of the disease [2]. HLA genes are probably the most important factors in genetic predisposition, as they play an important role in the presentation of the antigen, while other loci may be involved in an additive or epistatic way.

Involvement of multiple specificities of autoantibodies in the pathogenesis of PV is explained by the hypothesis of "multiple lesions" [3] as follows: anti-AChR antibodies (AChR - acetylcholine (ACh) receptors) trigger acantholysis, weakening the cohesion of neighboring keratinocytes by suppressing the physiological control of their polygonal shape and intercellular attachment. Affected keratinocytes compress, causing stratification in the intercellular space. Adhesion molecules, floating freely in the intercellular space, cause the mutual formation of antibodies-scavengers, which, in turn, saturate the epidermis, thereby preventing the formation of desmosomes by steric interference. Thus, according to the "multiple damage" hypothesis, PV arise as a result of synergistic and cumulative effects of autoantibodies directed at antigens of keratinocyte cell membranes of different types, including molecules that regulate the shape and adhesion of cells (AChR); molecules that provide cell adhesion (desmosomal cadherins). The severity of the disease and the exact clinical picture depend on the ratio of different types of autoantibodies in each patient [4].

Systemic administration of glucocorticosteroid hormones (GCS) is necessary to establish control over the disease in the acute stage [5]. Although GCS treatment saves lives, it can cause serious side effects, including death [6]. Therefore, patients with PV need drugs that can replace GCS. The development of nonsteroidal treatment is complicated by the lack of a clear understanding of the mechanisms that lead to keratinocyte detachment and death from vesicles. Literature data on recent advances in the field of understanding the autoimmune process of vesicles are sometimes contradictory, do not always correspond to existing dogmas, but the question of resolving all contradictions and developing new prospects for treatment remains relevant [7].

The aim of the study was to increase the effectiveness of treatment of patients with PV with the substantiation and development of modern methods of corrective therapy based on the study of indicators of changes in the balance of the thiol-disulfide system in the body of patients under pathological conditions and with prolonged use of high doses of glucocorticosteroid hormones.

Materials and research methods. There were examined 30 patients with PV (4 men and 26 women), who were hospitalized in KU "Zaporizhzhya Regional Skin and Venereal Clinical Dispensary" ZOR, Zaporizhzhia. At the time of observation, most of the patients were aged 61-70 years. As a comparison group, 20 practically healthy people were examined, constituting a control group.

Our studies were four-phase: before treatment; 2-3 weeks of maximum doses of GCS (stage I); 1.5-2 months before discharge from the hospital, when the patient was gradually reduced dose of systemic GCS and the selection of the optimal daily dose (stage II); after 5-6 months, when doses of GCS hormones were minimal (2-3 tablets) in the absence of clinical manifestations of vesicles (stage III).

The study was conducted in accordance with the basic bioethical norms of the "Declaration of Helsinki. World Medical Association Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects" (2000, as amended in 2008), the Universal Declaration on Bioethics and Human Rights (1997), the Convention on Human Rights and Biomedicine developed by the Council of Europe (1997). Written informed consent was obtained from each study participant.

The duration of the disease before hospitalization, according to the anamnesis, ranged from 3 weeks to 3 months. The diagnosis was established on the basis of clinical manifestations, course, cytological data (finding Tzanck cells (acantholytic cells)) and histological examinations. During the examination, the following concomitant pathology were detected in patients: atherosclerosis, angina pectoris (18 patients), gastrointestinal disorders (9 people), hypertension (22 patients), psychological disorders (7 patients).

Among patients with PV, women predominated (86.67%), and patients of the older age group – 43.33% were aged 61-70 years, 26.67% – 51-60 years.

There was a clear seasonality of recurrences of PV associated with the summer period. Thus, the process was exacerbated in April-May in 9 people (30%), in June-August in 21 people (70%).

According to the anamnesis of patients with PV, the following provoking moments were noted: stress – 4 patients, acute viral respiratory illnesses – 8, bath washing – 1,

insolation – 4, the remaining 13 patients the disease developed suddenly, against the background of good health.

Traditional therapy of patients with PV was based primarily on the appointment at the first stage of high (maximum) doses of GCS hormones in doses from 60 mg to 100 mg of prednisolone equivalent per day (12-20 tablets) according to age, sex, weight, concomitant and transferred pathology, 2/3 of the dose patients received in the morning in accordance with the physiological cycle of secretion of hormones of the adrenal cortex. After obtaining a pronounced therapeutic effect (absence of new vesicles, epithelialization of erosive areas) for 15-18 days reduced the daily dose of prednisolone by 5-10 mg every 5-7 days, and then – by 2.5-5 mg every 7-10 days to a maintenance dose of 10-15 mg per day until the minimum maintenance effective dose is reached, which provides remission of the disease for a long time (1-2 tablets per day). Sometimes with a benign course of the disease and the development of complete remission, the cancellation of hormones is possible.

Spectrophotometric determination of glutathione peroxidase (GPO) activity was performed. GPO catalyzes the oxidation reaction of glutathione with hydrogen peroxide. The principle of the method is based on determining the rate of formation of oxidized glutathione, the content of which is determined in the combined glutathione reductase reaction by the degree of oxidation of NADPH$^+$ at a wavelength of 340 nm. Next was spectrophotometric determination of glutathione reductase (GR) activity. The principle of the method is based on spectrophotometric determination of the amount of NADPH coenzyme consumed during the enzymatic reaction, which is calculated by the change in absorption at 340 nm.

The statistical data processing used the licensed program "STATISTICA® for Windows 6.1" (StatSoft Inc., USA, serial number RGXR412D674002FWC7). Data are presented as mean and standard error of representativeness of the sample mean (95% confidence interval (95% CI)). Comparison of groups on a qualitative basis, as well as in the study of the frequency of occurrence of indicators, was performed using the criterion χ^2 with the analysis of conjugation tables. The degree of correlation between pairs of independent traits, expressed in quantitative scales, was assessed using the Pearson (r) or P. Spearman (R) rank correlation coefficient, depending on the nature of the variable distribution.

Research results. Glutathione and enzymes of glutathione metabolism are extremely important in maintaining the functional activity of cells throughout the body. It was found that glutathione can directly modulate the proliferation of cells of various organs and systems of the body, including the skin. Cells depleted of glutathione do not fully develop a response to mitogens. Exogenous glutathione partially supports intracellular glutathione levels and

completely restores cell proliferation, while endogenous glutathione plays a key role in metabolic reactions associated with DNA synthesis and mediates the effects of exogenous thiols. The metabolic role of glutathione and enzymes of glutathione metabolism is also associated with antioxidant processes. It is assumed that the synthesis and reduction of glutathione through glutathione reductase provides full effector functions of the immune system, which are aimed at eliminating damaged and non-viable cells of the body, and low activity of xenobiotic biotransformation enzymes leads to a change in immune homeostasis due to the formation of reactive metabolites of xenobiotics with their subsequent non-covalent binding to cell macromolecules and the formation of "conjugated antigens".

When examining healthy people from the control group, we determined that glutathione reductase was at the level of 11.28 ± 0.19 mkm / mg protein / min ($p<0.05$), in patients with PV glutathione reductase was 6.44 ± 0.59 mkm / mg protein / min, and was 75.16% lower than the similar marker of the previous group ($p<0,05$).

The value of glutathione peroxidase in people from the control group was 70.18 ± 7.24 mkm / mg protein / min ($p<0.05$), exceeding the same group of patients with PV by 81.20%. Glutathione peroxidase in patients with PV was at the level of 38.73 ± 3.27 mkm / mg protein / min.

Against the background of the main stages of the pathological process of the skin in patients with PV there was a significant decrease in the level of reduced glutathione (GSH), it was determined at 0.65 ± 0.06 mkm / mg protein, and the difference in percentage compared to healthy people was 67.69 % ($p<0.05$).

There was also an increase in the values of oxidized glutathione (GSSG) in the group of patients with PV, the values of this marker of thiol disulfide balance were determined at 0.54 ± 0.05 mkm / mg protein, exceeding the same control group by 45.95% ($p<0.05$).

The result of the violation was equalized between oxidized and reduced thiols on the background of the pathological process of PV before the pathogenetic therapeutic course using GCS in patients there was a decrease in the level of reduced thiols to values of 5.03 ± 0.57 mM / mg protein, the percentage difference between this group and marker of healthy people was 104.37% ($p<0.05$).

Characteristic changes in the balance of the thiol disulfide system under conditions of activation of oxidative and nitrosative stresses to therapeutic measures include an increase in oxidized thiols in the group with PV: oxidized thiols were at the level of – 15.48 ± 1.26 mM / mg protein ($p < 0.05$), reflecting the severity of the pathological process, and exceeding similar indicators of the control group by 76.91%.

Thus, we obtained indicators of thiol-disulfide balance before therapeutic measures, which indicated that against the background of PV there was a significant increase in oxidation markers: oxidized glutathione and oxidized thiols; and reducing the level of markers of reductive processes: glutathione reductase, glutathione peroxidase, reduced glutathione, reduced thiols. These changes systematically reflect the reaction of the antioxidant system of the human body in the pathology of PV – the development of deprivation of the glutathione chain of the thiol-disulfide system by activating oxidative and nitrosative stress and decompensation of the antioxidant system as a whole with damage to key cells and organs.

The positive effect of prescribed GCS was noted in our study on the state of the components of the glutathione chain of the thiol-disulfide system, which manifested itself in an increase in the amount of reduced glutathione, reduced SH-groups, increased activity of GR and GPO on the background of reduced levels of oxidized glutathione.

After a course of therapy with systemic GCS in patients with PV in the third stage, we found an increase in glutathione reductase levels to 15.47 ± 1.26 mkm / mg protein / min (p <0.05), in patients with PV in the second stage, this marker was determined at the level of 10.83 ± 0.99 mkm / mg protein / min, and the difference between these groups was 42.84%. When examining patients with PV after the first stage of GCS glutathione reductase was 8.51 ± 0.87 mkm / mg protein / min, and was 81.79% lower than the similar marker of patients with PV after the third stage and 27.26% lower compared with the second stage ($p<0.05$).

Also there were recorded an increase in glutathione peroxidase after hormonal pathogenetic treatment in the group of patients with PV after the third stage to 95.19 ± 9.11 mkm / mg protein / min ($p<0.05$), this value was the highest among the examined groups of patients of all three stages, exceeding the same indicator of the second stage by 31.22% and the first stage by 91.11%. Glutathione peroxidase in the second stage of treatment was at the level of 72.54 ± 7.18 mkm / mg protein / min, and in the first was observed at the level of 49.81 ± 5.14 mkm / mg protein / min ($p<0.05$), the difference between the levels of this marker at these stages was 45.63%.

Our pathogenetic therapy of GCS significantly led to an increase in the level of reduced glutathione (GSH), so in particular after the third treatment stage it was at 1.52 ± 0.13 mkm / mg protein, exceeding the same rate of the first and second stages of GCS administration by 87.65 and 61.70%, respectively ($p<0.05$). In the group of patients with PV in the second stage, reduced glutathione was determined at the level of 0.94 ± 0.09 mkm / mg protein, and in the first stage – 0.81 ± 0.08 mkm / mg protein, and the percentage difference between these stages was 16.05% ($p<0.05$).

There were also depression of oxidized glutathione (GSSG) at all stages of treatment with GCS drugs, the highest values of this marker of thiol-disulfide balance were determined in patients after the first stage of GCS – 0.42 ± 0.05 mkm / mg protein, exceeding the third stage by 100%, and the second stage – by 10.53% (p<0.05). The value of oxidized glutathione in the second stage of treatment was 0.38 ± 0.04 mkm / mg protein, and in the third – 0.21 ± 0.03 mkm / mg protein, the percentage difference between these stages was 80.95% (p<0.05).

The course of GCS therapy in patients with PV contributed to the fact that the level of reduced thiols increased significantly during each stage of therapy of the examined patients, in particular in the third stage of maintenance GCS therapy reduced thiols were determined at 15.64 ± 1.23 mM / mg protein, exceeding this marker of the second stage by 36.95%, and the value of reduced thiols of the first stage by 83.78% (p<0.05). The value of reduced thiols of the group of patients with PV in the second stage was 11.42 ± 1.08 mM / mg protein, and in the first stage – 8.51 ± 0.92 mM / mg protein, the percentage difference between these therapeutic stages was determined in 34.19% (p<0.05).

During the first stage of administration of significant doses of GCS to patients with PV oxidized thiols showed a decrease after our treatment, but compared with other stages were at the highest level – 11.57 ± 1.02 mM / mg protein (p<0.05), reflecting severity of the pathological process, and exceeding similar indicators of the second and third stages by 22.05 and 85.12%, respectively. In patients of the third stage, oxidized thiols were at the lowest level – 6.25 ± 0.69 mM / mg protein (p<0.05), and in the second – at the level of 9.48 ± 0.91 mM / mg protein, the percentage difference between these stages is 51.68%.

Thus, we can summarize: our prescribed systemic GCS therapy of patients with PV during each stage of administration of different doses of drugs led to the restoration of the balance of thiol-disulfide system, which manifested itself in the form of reduced oxidation markers: oxidized glutathione and oxidized thiols; as well as in the elevation of markers of restorative processes – glutathione reductase, glutathione peroxidase, reduced glutathione, reduced thiols, having a systemic positive effect on the pathological process and leading to remission of the disease clinically.

Discussion of the obtained results. PV is diseases in which there are no absolute contraindications to GCS therapy, as only these drugs can prevent the death of patients. High-dose long-term systemic GCS therapy remains the basis of modern therapy in patients with PV. GCS hormones are needed to control PV during the acute stage [8]. The optimal dosage was variable and could not be predicted from the outset for any patient. Some patients respond quickly and completely to treatment with moderate doses of prednisone orally (1 mg /

kg / day), others are quite refractory and require much higher doses. If after 5-7 days there is no answer, the dose is increased by 50-100% [9]. After achieving control of the disease (absence of new lesions, epithelialization of existing erosions and Nikolsky's sign is usually negative) [10], the dosage of prednisone is reduced "logarithmically", by 10-20% every 7-15 days. Patients with PV with exacerbation are treated as as well as new patients with PV, the dose of prednisone is increased to achieve control of the disease and then reduced.

The first report about administration of GCS to a patient with PV dates back to 1940 [11], approximately 25 years before antibodies to PV were detected. Adrenocortical extract was tested for treatment because it was observed that PV are associated with changes in the chemical composition of the blood of patients characteristic of abnormal (insufficient) function of the adrenal glands that produce GCS. Synthetic cortisone was introduced to treat PV after about 10 years. Prior to the introduction of oral GCS therapy in the 1950s, the disease had a severe natural course with 50% mortality after 2 years and 100% mortality 5 years after the onset of the disease. Although there is currently a significant reduction in mortality [12], it remains at a relatively high level, about 12%, and death is almost always associated with complications of therapy.

Early side effects of systemic GCS, which are essentially inevitable, include increased appetite, fluid and salt retention, leading to weight gain and psychoneurological disorders such as emotional lability, insomnia, irritability, anxiety, depression, euphoria, hyperactivity, and manic episodes. Delayed and latent cumulative dose-dependent side effects include Cushingoid, hypothalamic-pituitary-adrenal syndrome, menstrual irregularities, hyperlipidemia, atherosclerosis, cardiovascular disorders, liver obesity, cataracts, growth retardation, osteoporosis, osteonecrosis, muscle weakness, myopathy, bruising and skin thinning [13]. Rare and unpredictable side effects are glaucoma, pancreatitis and cerebral edema. Treatment of patients with PV with GCS can also expose or worsen comorbidities: acne vulgaris, diabetes and hypertension.

The aim of the PV study is to develop an effective treatment that would achieve and maintain clinical remission without the need for systemic GCS. Although this goal has not yet been achieved, significant progress has been made in developing regimens that reduce steroid doses. Assuming that GCS treat PV due to their immunosuppressive properties, most clinical studies have focused on immunosuppressive therapy. The following is a chronological sequence of reports of steroid-lowering drugs and treatments for PV. Immunosuppressive cytotoxic drugs are: methotrexate, azathioprine, cyclophosphamide, chlorambucil and mycophenolate mofetil. Immunomodulators are: heparin, cyclosporine, T-cell

immunocorrection by photophoresis, high-dose intravenous γ-globulin, rituximab and daclizumab. Anti-inflammatory drugs are: gold, dapsone, doxycycline, tetracycline, minocycline, tranilast and thalidomide. Extracorporeal autoantibody extractions are: plasmapheresis, plasma transfusion, hemocarbofiltration and immunoadsorption of protein A [14].

Unfortunately, these treatments do not reliably control acute PV without systemic GCS, indicating that in addition to immunosuppression, the therapeutic effect of GCS in PV includes other mechanisms, such as direct anti-acantholytic action on keratinocytes. Moreover, although there is ample evidence that PV is predominantly an autoimmune disease of the Th2 type, at least in terms of production anti-Dsg 3, data on the mechanisms of immunomodulatory action of GCS illogically demonstrate that these drugs stimulate Th2 polarization of CD4+ T-cells [15].

Direct anti-acantholytic effects of GCS methylprednisolone and hydrocortisone on keratinocytes were found in vitro experiments in which high doses of these drugs blocked acantholysis caused by PV IgG [16]. Because antibody-producing cells were not present in the cultures, these drugs could not exert their anti-acantholytic effects by affecting lymphocytes. Subsequent in vivo experiments showed that the introduction of methylprednisolone significantly reduced the degree of acantholysis in the epidermis of nude mice for 3-5 days, which were administered PV IgG. This is consistent with clinical observations that blistering in patients with PV ceases within 24-48 hours after the start of high-dose pulse therapy with methylprednisolone or dexamethasone, while there is a significant decrease in autoantibody titers 3-4 weeks after starting GCS therapy [17]. It is well known that PV therapy clinically improves the course of the disease before lowering antibody titers.

In addition, topical administration of 0.05% clobetasol propionate cream may initially control skin lesions in simple patients with PV [18]. Direct effects of GCS that can protect keratinocytes from PV IgG may include changes in gene expression, as shown by DNA microarray analysis. PV IgG were suppressed, and methylprednisolone increased the expression of genes encoding adhesion molecules of keratinocytes Dsg 3 and periplakin, regulators of cell cycle progression and apoptosis, markers of differentiation, protein kinases and phosphatases, serine proteases and others. In addition, methylprednisolone blocked the phosphorylation of Dsg 3, E-cadherins and β- and γ-catenins induced by PV IgG [19].

These pharmacological effects of methylprednisolone help to explain the dose-dependent therapeutic effect of GCS in patients with PV. It is well known that extremely high

doses of GCS are sometimes required to achieve control of acantholysis in the acute stage of the disease. Thus, in addition to their immunosuppressive and anti-inflammatory effects in PV, GCS can also regulate the adhesion and viability of keratinocytes through a combination of their genomic and non-genomic effects.

Therefore, GCS remain an important component of PV treatment. Early and maximum possible use of GCS is necessary to reduce the duration of treatment and prevent recurrence. In the future, in the therapeutic regimen of PV, adjuvant drugs will reduce the total dose of GCS, and the course of PV can be improved with new treatments.

Conclusions. The indicators of thiol-disulfide balance obtained by us before carrying out therapeutic measures testify that against the background of the pathological process of PV there are a significant increase in oxidation markers: oxidized glutathione and oxidized thiols; and reducing the level of markers of reducing processes: glutathione reductase, glutathione peroxidase, reduced glutathione, reduced thiols. These changes systematically reflect the response of the antioxidant system of the human body in the conditions of PV pathology – the development of deprivation of the glutathione chain of the thiol-disulfide system by activating oxidative and nitrosative stress and decompensation of the antioxidant system as a whole with the development of damage to key cells and organs.

Appointment to patients with PV systemic GCS for three stages – for 2-3 weeks taking the maximum doses of GCS (stage I); 1.5-2 months before discharge from the hospital, gradual reduction of the dose of systemic GCS and selection of the optimal daily dose (stage II); after 5-6 months hormone doses were minimal (2-3 tablets) in the absence of clinical manifestations of PV (stage III) led to the restoration of the balance of the thiol-disulfide system in patients, which manifested itself in the form of reduced oxidation markers: oxidized glutathione and oxidized thiols; as well as in the elevation of markers of restorative processes – glutathione reductase, glutathione peroxidase, reduced glutathione, reduced thiols, having a systemic positive effect on the pathological process, which was reflected in the normalization of laboratory parameters of patients and clinically in the form of stable remission.

Conflicts of interest. Author has no actual or potential conflicts of interest.

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