ORIGINAL ARTICLE

RETROSPECTIVE CHART ANALYSIS OF PATIENTS DIGNOSED WITH ACANTHOLYTIC PEMPHIGUS FOR THE PERIOD 2008-2018

DOI: 10.36740/WLek202202116

Yanina Kutasevych, Aliya Abdalla, Iryna Oliinyk, Iryna Mashtakova, Yuliia Shcherbakova
INSTITUTE OF DERMATOLOGY AND VENEREOLOGY OF NAMS OF UKRAINE, KHARKIV, UKRAINE

ABSTRACT

The aim: Determine the clinical and anamnestic criteria that cause the acantholytic pemphigus (AP) morbidity in the course of the treatment.

Materials and methods: Analysis of medical histories of patients who underwent the therapy on the basis of the clinic for 10 years. In the analysis of 174 medical case histories were determined the factors provoking the onset and exacerbation of the disease. The disease severity was assessed using the IKEDA index.

Results: During the analysis, patients were divided into two groups. The I group - patients who required combination therapy - systemic glucocorticosteroids (SGCs) and immunosuppressant (azathioprine (AZA)). For patients of group II used SGCs - according to the indications. The presence of intoxication and signs of pyoderma were more common in patients of group I. The number of exacerbations per year for an unknown reason in group I was almost 3 times higher. The ineffectiveness of high starting doses of SGCs was 20.2% of cases compared with those in group II.

Conclusions: According to clinical and anamnestic data, during the retrospective analysis of case histories, the criteria determining the severity of acantholytic pemphigus during treatment were determined: the age of patients, the diagnosis period, the prevalence of lesions and severity of dermatosis according to the IKEDA index, the selection of adequate treatment tactics, taking into the complications caused as a result of the systemic glucocorticosteroids therapy.

KEY WORDS: acantholytic pemphigus, retrospective analysis, systemic glucocorticosteroid therapy, immunosuppressive therapy

Wiad Lek. 2022;75(2):416-421

INTRODUCTION

Acantholytic pemphigus (AP) belongs to a group of particularly severe skin and/or mucosal diseases that lead to disability or death [1]. This is an autoimmune disease whose morphological feature is acantholysis induced by autoantibodies to desmosomal proteins of keratinocytes [2].

Before the advent of steroids, the mortality rate reached almost 100%. From 1950 to the present day, mortality has decreased 10 fold due to the use of SGCs [3].

In terms of prevalence, the global average incidence of AP is low and is regionally dependent. Thus, in European countries it is as follows: Finland – 0.08, France – 0.17, Bulgaria – 0.47 and Greece – 0.93 cases per 100 thousand population. AP is most common in Jews and people of Mediterranean and Middle East origin. In Israel, the incidence of pemphigus reaches 1.62, in Tehran – 1.6, in Iran – 1.0 cases per 100 thousand population, which is much higher than in Europe. [4].

It is important to note that the grave condition of patients with this pathology occurs due to the impaired skin barrier function and mucous membranes, secondary infection, loss of biologically active trace substances, fluid, protein, carbohydrate and lipid metabolism, which promotes the vicious loop of pathogenesis. The development of intoxication, septicemia, etc. in the absence of pathogenetic therapy affects the somatic condition. The combination of the above factors is the foundation of disability and mortality among patients of the given nosology [5]. High doses of SGCs, the duration of their use has side effects caused by the endocrine system [6, 7], cardiovascular system [8, 9], gastrointestinal tract [10], musculoskeletal system [11, 12], skin, eye diseases [13], psycho-neurological disorders [14], changes in the water-electrolytic composition of blood [9]. All the above-mentioned aggravates the progression of dermatosis.

Current methods of treating AP, to date, do not always have a positive effect on the disease progression. Determining the clinical and anamnestic criteria, which cause the pemphigus morbidity in the course of the treatment, will contribute to the prescription of adequate therapy in the early stages of observation, which will be of great medical and social importance.

THE AIM

Analyze the factors that contributed to the onset of acantholytic pemphigus (AP) and trigger factors for exacerbation of dermatosis, the number of relapses per year, age and gender dependence for the correction of therapeutic tactics, taking into account the severity of the dermatological process and comorbid conditions.

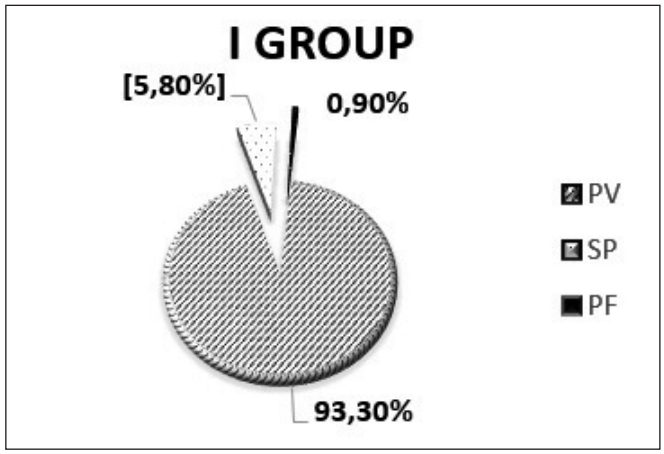

Fig. 1. Clinical forms of group I

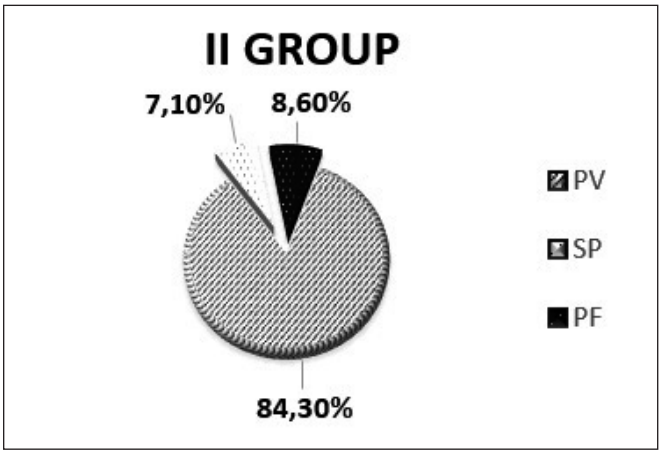

Fig. 2. Clinical forms of group II

MATERIALS AND METHODS

A retrospective analysis of the archival material of medical histories of patients diagnosed with AP who were treated in the dermatological department of the SE "IDV OF NAMS of UKRAINE" in Kharkiv for 10 years (period 2008 - 2018) was conducted.

In the analysis of 174 medical case histories, they determined the factors provoking the onset and exacerbation of the disease; the disease duration at the time of hospitalization in the clinic and the timing of diagnosing the AP since the onset of primary rash; recorded the primary location of the rash, analyzed the previously established diagnoses; the therapy assigned based on these diagnoses; the specialists consulted by patients in the first instance; assessed the general condition of patients at the time of hospitalization; took into account the starting dose of SGCs depending on the dermatosis severity; determined the number of exacerbations per year, the cause of their occurrence and the dose of SGCs that triggered exacerbations.

The disease severity was assessed using the IKEDA index [15]. The following parameters were studied: the area of skin lesions, the presence or absence of rashes on the mucous membranes, the severity of Nikolskyi's symptom and the number of new vesicles caused per day. Each of the parameters was evaluated on a four-point scale from 0 to 3 points. The maximum value of the IKEDA index constitutes 12 points. The following forms of the disease were estimated by the sum of points: 12-8 points – severe form, 5-7 points – moderate form and <5 points - mild form [15, 16]. During the cytological examination, the acantholytic cells (AC) in smears taken from the vesicle bottom/erosion, namely their presence, number and morphological characteristics, taking into account the severity of dermatosis, were evaluated.

Thus, the initial dose of SGCs was specifically prescribed taking into account the severity, the weight, and the concomitant somatic pathology. In terms of prednisolone, the daily dose ranged from 160 to 45 mg. Patients with a severe course of disease received 160-100 mg/d, patents with a moderate course of disease received 100-60 mg/d, and those with a mild course were given 60-45 mg/d. Preference was given to the combined method of administering medication, namely intramuscularly and orally each having different effect.

The results of bacteriological examination of the skin area affected by vesicles and/or erosions (for cause) were evaluated.

RESULTS

In a retrospective analysis, 174 case histories of patients diagnosed with AP were divided into 2 groups according to treatment tactics. The first group had 104 case histories, where patients had received SGCs and AZA. The second group had 70 case histories in the treatment of which they used the SGCs therapy.

In the I group, patients according to anamnestic data in 93.3% of cases (97 out of 104) were diagnosed with PV, SP – in 5.8% of cases (6 out of 104) and PF in 0.9% of cases (1 out of 104) (Fig. 1A). The mean age of patients was 50.8 ± 1.3 (25 to 80 years). The ratio of women/men was 2/1. The average duration of the disease was 5.8 ± 0.4 years. The term of establishing the diagnosis was 6.7 ± 0.2 months (Fig. 2). Primary rash in almost 79% of cases (82 cases out of 104) was observed on the mucous membranes and the vermilion border, so patients received therapy from dentists for stomatitis of various origins and otorhinolaryngologists. For the treatment of seborrheic and allergic dermatitis, toxicoderma, family doctors prescribed systemic prolonged steroid drugs.

The cause of the disease onset was noted to be stress - 28.8% (in 30 cases out of 104), SARS – 24.0% (25 cases out of 104), dental treatment - 10.6% (11 cases out of 104). In 3.9% cases (4 of 104), the onset of dermatosis was associated with other factors (sun insolation, vaccination, chemotherapy for lymphocytic leukemia). It was not possible to establish the cause of the rash in 32.7% of patients (34 of 104) (Fig. 3).

At the time of hospitalization, patients of I group, by severity were distributed as follows: in 30.8% (32 out of 104) cases, severity was recorded (12-8 points according to the IKEDA index), in 52.9% cases (55 of 104) – moderate

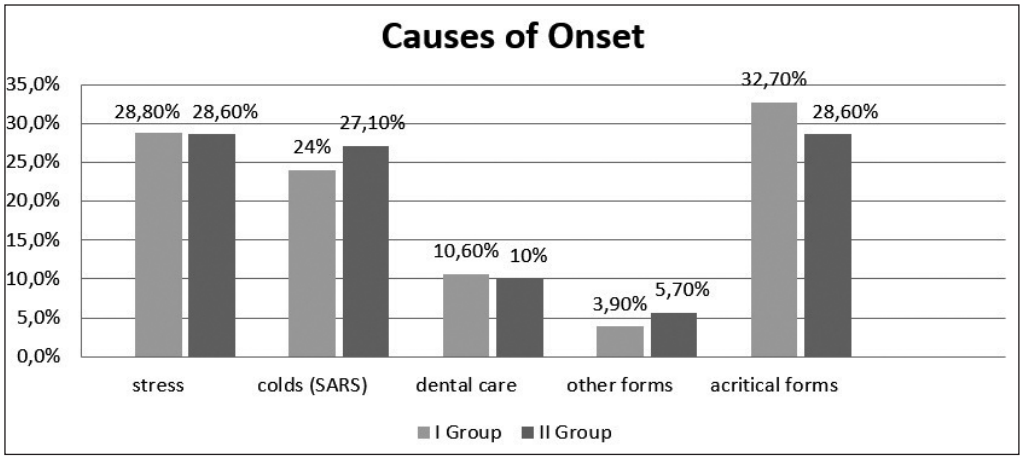

Fig. 3. Causes of dermatosis onset in groups I and II

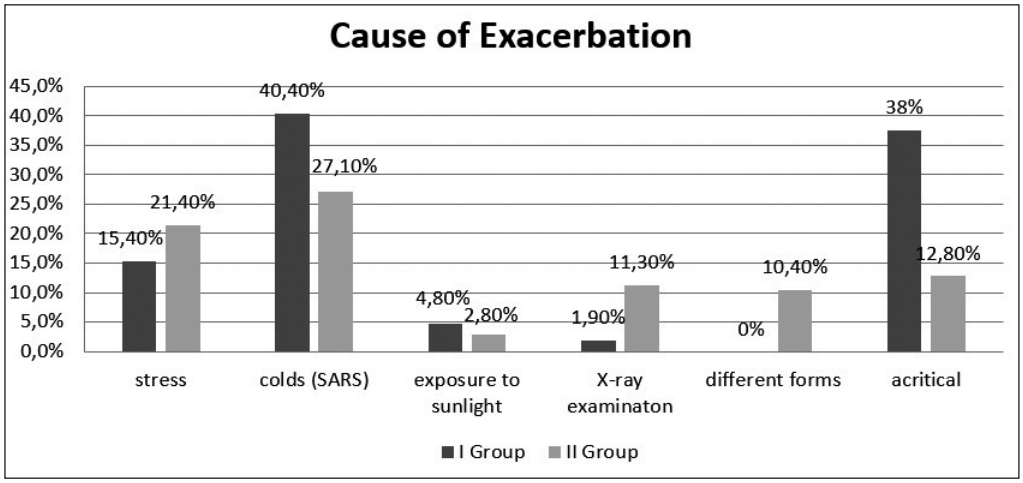

Fig. 4. Causes of dermatosis exacerbation in groups I and II

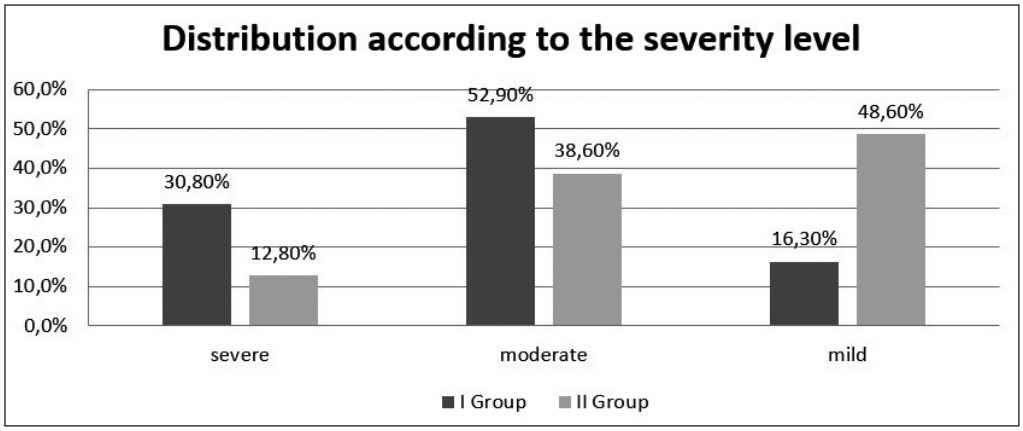

Fig. 5. Distribution of dermatosis by severity among patients of groups I and II

disease course (5-7 points) and mild disease course (<5 points) in 16.3% of cases (17 out of 104) (Fig. 4).

At cytological examination from the bottom of erosive surfaces in 62.5% of cases (65 out of 104) ACs were present. According to the analysis of cytological examination for identifying ACs, by severity it had the following form: in patients with a severe course of disease, ACs were revealed in almost 28.0% of cases (29 out of 104) that were located in layers. In 31.7% cases (33 out of 104) along with moderate severity of and in 2.9% (3 of 104) of mild cases.

Signs of pyoderma were observed in 59.6% (62 of 104) of cases: 16.3% (17 cases out of 104) – severe, 34.6% (36 cases out of 104) – moderate, 8.7% (9 cases out of 104) – mild.

The intoxication syndrome was diagnosed in 54.8% of cases (57 case histories out of 104): 15.4% (16 out of 104 cases) - patients with severity, 32.7% (34 out of 104 cases) – moderate severity and 6.7 % (7 out of 104 cases) – mild severity. Clinical manifestations of the intoxication syndrome were diagnosed in the form of chills and fever, muscle and joint pain, general weakness, subfebrile and febrile fever, the presence of hypotension and tachycardia, tachypnea, sleep disturbances. It was laboratory-confirmed by neutrophilic leukocytosis and increased ESR.

The starting dose of SGCs was 160-60 mg/d of SGCs depending on the distribution of the skin process, the patient's weight, and the available accompanying somatic pathology

Fig. 6. Comparison of performance of both groups

(Fig. 2). Lack of therapeutic effect of high doses of SGCs in the first 7-10 days was observed in 20.2% (21 cases out of 104). The cytologic picture retained the previous characteristics. When trying to reduce SGCs by 15-20% of the maximum starting dose, exacerbation occurred in 21.2% (22 of 104 cases). When observing cytological drugs in the dynamics, there was an increase in the number of AC while maintaining morphological characteristics (due to the influence of glucocorticoid drugs). In 58.6% of cases (61 cases out of 104), in the 2nd week of treatment there was noted stabilization of the skin process. When reducing the dose of SGCs to 37.5 - 35 mg/d over a period of 2 - 3 months from the date of patient's discharge there was noted an exacerbation of dermatosis in these patients. Dermatosis was common; severity was found. The patient required hospitalization. In each case, patients in this group in addition to SGCs therapy were prescribed AZA at a dose of 100-50 mg/d.

According to the analysis of factors contributing to the exacerbation of the disease, psycho-emotional overload was indicated in 15.4% (16 case histories out of 104), colds – 40.4% (42 case histories out of 104), solar insolation – 4.8% (5 case histories out of 104), X-ray examination – 1.9% (2 case histories out of 104). The exacerbating factor could not be established in 37.5% (39 cases out of 104) (Fig. 5).

Indications for prescription of AZA were the following: lack of therapeutic effect of SGCs therapy; the appearance of new lesions when trying to gradually reduce the dose of SGCs; exacerbation of dermatosis during the first year.

The II group included 70 case histories of patients with AP in the treatment of which they used SGCs drugs. PV was established in 59 cases out of 70 (84.3%), PF – 6 cases out of 70 (8.6%) and PS – 5 case histories out of 70 (7.1%) (Fig. 1B). In most cases, the primary rash was localized on the mucous membranes – 70.0% (49 cases out of 70). Patients, as with group I, received therapy for stomatitis. According to anamnestic data, patients aged 26 to 79 (mean age 54 ± 1.4) in the ratio of women/men 1.7/1. The diagnosis period lasted 5.5 ± 0.3 months. Over time, the average duration of dermatosis was equal to 7.0 ± 0.6 years in the above-mentioned group of patients (Fig. 2).

The cause of the primary rash was psycho-emotional overload in 20 cases out of 70 (28.6%), colds (SARS) in 19 case histories out of 70 (27.1%). The presence of rash after dental treatment was noted in 7 of 70 cases (10.0%). Excessive sun exposure and burns were reported in 4 cases out of 70 (5.7%). It was not possible to determine the cause of the rash in 20 out of 70 cases (28.6%) (Fig. 3).

According to the status localis assessment, severe dermatosis (12-8 points) was noted in 12.8% (9 cases out of 70), medium (7-5 points) – in 38.6% (27 out of 70) and mild (<5 points) – in 48.6% (34 out of 70 cases) (Fig. 4).

Cytological examination of the material obtained from the bottom of the rash foci revealed AC in 18 cases out of 70, which constituted almost 25.7%. In the case histories of patients with a severe disease course – 5.7% (4 cases out of 70), medium – 17.1% (12 cases out of 70) and mild – 2.9% (2 cases out of 70), AC had different quantitative and morphological signs depending on the severity of dermatosis.

Signs of pyoderma were observed in 17 out of 70 cases (24.3%): in 5 cases out of 70 with a severe course – 7.1%; 8 out of 70 cases (11.4%) – moderate and 4 case histories out of 70 (5.7%) – mild.

With intoxication syndrome were observed in 11 cases out of 70 (15.7%): 4 case histories out of 70 (5.7%) – severe and in 7 cases out of 70 (10.0%) – moderate. Patients with mild dermatosis had no signs of intoxication.

According to the distribution of the skin process, the weight, and the concomitant somatic pathology, the starting dose of SGCs ranged from 120 to 45 mg/d (Fig. 2). Assessing the course of the disease, it was found that new vesicles did not form on the 5-7th day of treatment. In the second week of treatment there were signs of erosion inlay (dense multilayered crusts were formed whose edges were raised on the periphery and epithelialization was observed), negation of Nikolsky's symptom was observed and a program of gradual reduction of SGCs to 25-20 mg/d was started for 9-12 months under the supervision of a district dermatologist.

Exacerbations occurred in 1-2 years after discharge from hospital. The reasons included: SARS – in 19 cases out of 70 (27.1%); stress was observed in 15 case histories out of 70

(21.4%); refusal of basic maintenance therapy in 10 cases out of 70 (14.2%); radiological irradiation was noted in 8 cases out of 70 (11.3%); unsystematic use of NSAIDs 4 cases out of 70 (5.6%). The use of penicillin antibiotics provoked an exacerbation in 3 cases out of 70 (4.8%) and solar exposure was indicated in 2 case histories out of 70 (2.8%). The cause of dermatosis exacerbation could not be determined in 9 cases out of 70 cases (12, 8%) (Fig. 5).

To date, 80.7% of patients have a disability based on the following diagnosis: AP corticosteroid dependent form. It is known that 8.8% of patients died within the first 7 years after the onset of primary dermatosis manifestations due to complications caused by the SGCs therapy.

DISCUSSIONS

According to clinical and anamnestic data, during the retrospective analysis of case histories, the criteria determining the severity of AP during treatment were determined: the age of patients, the diagnosis period, the prevalence of lesions and severity of dermatosis according to the IKEDA index [15], the selection of adequate treatment tactics, taking into the complications caused as a result of the SGCs therapy [10].

Thus, it was found that patients of group I were younger than persons of group II by 3.2 ± 0.2 years, and despite this, in terms of the severity of clinical manifestations and the course of AP, they prevailed in patients of group I (30.8% in group I versus 12.8% in group II).

The period of diagnosis establishment in patients of group II was shorter, varying up to 6 months, which makes it possible to state the typicality of the clinical picture and course in this group of patients. The prescription of SGCs to patients had taken place earlier and did not lead to steroid resistance. Thus, in group II, the number of patients with a severe disease course was lower by 20.0% than in patients of group I.

The presence of intoxication and signs of pyoderma were more common in patients of group I receiving therapy with prescription of SGCs and AZA. The number of exacerbations per year for an unknown reason in group I was almost 3 times higher. The ineffectiveness of high starting doses of SGCs was 20.2% of cases compared with those in group II.

The analysis of case histories showed the impossibility of achieving the level of maintenance dose of SGCs without prescription of additional immunosuppressive therapy in 79.8% of cases for group I.

The above factors complicate the course of dermatosis due to the prevalence of dermatosis, the presence of bacterial complications [5, 6], loss of biologically active trace substances, fluid, protein, carbohydrate and lipid metabolism [8, 9], the development of resistant forms to SGCs [11, 17]. As a consequence to high doses of immunosuppressive therapy which leads to disability and mortality in some cases were showed in previous studies [3, 17].

CONCLUSIONS

Analysis of case histories of patients with AP who received medical care in the dermatological department of the SE "IDV OF NAMS of UKRAINE" in Kharkiv for the period 2008-2018 showed the impossibility of achieving the level of maintenance dose of SGCs without the appointment of additional immunosuppressive therapy in 41.4% of cases of patients of group I in the first three months of therapy and in 58.6% of cases of patients of group I in the second half a year. While patients of group II reached a maintenance dose of basic therapy of 25-20 mg / d during the first 3 months and did not have exacerbation of dermatosis during the first year if the recommendations are followed.

Clinical signs of steroid resistance in patients were established: the appearance of new elements at a high dose of SGCs - AZA was prescribed in the second week after hospitalization; the appearance of new blisters with a gradual decrease in the dose of SGCs by 15-20% of the initial - AZA was prescribed for 3-4 weeks of treatment; exacerbation from 2 times a year during the first year.

REFERENCES

1. Porro A.M., Filho G.H., Santi C.G. Consensus on the treatment of autoimmune bullous dermatoses: pemphigus vulgaris and pemphigus foliaceus – Brazilian Society of Dermatology. Bullous dermatoses An Bras Dermatol. 2019;94(2): 20-32.
2. Spindler V., Waschke J. Pemphigus — a disease of desmosome dysfunction caused by multiple mechanisms. Front. Immunol. 2018;9:136:1-8. doi: 10.3389/fimmu.2018.00136.
3. Tavakolpour S. Current and future treatment options for pemphigus: Is it time to move towards more effective treatments? Int Immunopharmacol. 2017;53:133–142. doi: 10.1016/j.intimp.2017.10.027.
4. Kasperkiewicz M., Ellebrecht C.T., Takahashi H. et al. Pemphigus. Nat Rev Dis Primers. 2017;11(3):17026. doi: 10.1038/nrdp.2017.26.
5. Ren Z., Narla S., Hsu D.Y. et al. Association of serious infections with pemphigus and pemphigoid: analysis of the Nationwide Inpatient Sample. J Eur Acad Dermatol Venereol. 2018;32(10):1768-1776. doi: 10.1111/jdv.14961.
6. Stevens N.E., Cowin A.J., Kopecki Z. Skin Barrier and Autoimmunity-Mechanisms and Novel Therapeutic Approaches for Autoimmune Blistering Diseases of the Skin. Front Immunol. 2019;10:1089. doi: 10.3389/fimmu.2019.01089.
7. Kim E.J., Kim J.J. Amygdala, Medial Prefrontal Cortex and Glucocorticoid Interactions Produce Stress-Like Effects on Memory. Front. Behav. Neurosci. 2019;13:210. doi: 10.3389/fnbeh.2019.00210.
8. Yaghubi E., Daneshpazhooh M., DJalali M. et al. Effects of l – carnitine supplementation on cardiovascular and bone turnover markers in patients with pemphigus vulgaris under corticosteroids treatment: A randomized, double – blind, controlled trial, Dermatologic Therapy. 2019;32(5):e13049. doi: 10.1111/dth.13049.
9. Whitworth J.A. Mechanisms of glucocorticoid-induced hypertension. Kidney Int. 1987; 31 (5): 1213-1224.
10. Schadt C. Glucocorticoids. Dermatology. 4th ed. Philadelphia: Elsevier. 2017, 2199 p.
11. Zhao Z., Xue Y., Hong D. et al. Polymorphisms in the Glucocorticoid Receptor Gene and Associations with Glucocorticoid-Induced Avascular Osteonecrosis of the Femoral Head. Genet Test Mol Biomarkers. 2017; 21 (5): 322-327. doi: 10.1089/gtmb.2016.0260.
12. Chotiyarnwong P., McCloskey E. Pathogenesis of glucocorticoid-induced osteoporosis and options for treatment. Nat Rev Endocrinol. 2020; 16:437–447. doi:10.1038/s41574-020-0341-0.

13. Kridin K. Emerging treatment options for the management of pemphigus vulgaris. Ther Clin Risk Manag. 2018; 14: 757-778. doi: 10.2147/TCRM.S142471.
14. Kridin K., Zelber-Sagi S., Comaneshter D. et al. Association Between Pemphigus and Neurologic Diseases. JAMA Dermatol. 2018; 154 (3): 281-285.
15. Ikeda S., Immamara S., Hashimoto I. et al. History of the establishment and revision of diagnostic criteria, severity index and therapeutic guidelines for pemphigus in Japan . Arch Dermatol Res. 2003;1: 12-16.
16. Krain R.L., Kushner C.J., Tarazi M. et al. Assessing the correlation between disease severity indices and quality of life measurement tools in pemphigus. Front. Immunol. 2019;10:2571. doi: 10.3389/fimmu.2019.02571.
17. Gangan R. Refractory pemphigus vulgaris: Treatment options. Journal of Skin and Sexually Transmitted Diseases. 2019; 1(2):61-65.

ORCID and contributionship:
Yanina Kutasevych: 0000-0001-8706-1487[A,F]
Aliya Abdalla: 0000-0002-6180-549X[A-D]
Iryna Oliinyk: 0000-0002-6408-830X[B,D,F]
Iryna Mashtakova: 0000-0002-3592-6896 [B,E]
Yuliia Shcherbakova: 0000-0002-3682-7451[B,E]

Conflict of interest:
The Authors declare no conflict of interest.

CORRESPONDING AUTHOR
Aliya Abdalla
Institute of Dermatology and
Venereology of NAMS of Ukraine
7/9 Chernyshevska st., 61057, Kharkiv, Ukraine
tel: +380506421238
e-mail: aliya.abdalla04@gmail.com

Received: 03.03.2021
Accepted: 28.08.2021

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article