ORIGINAL INVESTIGATIONS

Glucocorticoid toxicity index in patients with systemic lupus erythematosus (preliminary data)

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Objective: *to investigate the contribution of glucocorticoids (GC) to the development of irreversible organ damage in patients with systemic lupus erythematosus (SLE) using the GC toxicity index (GTI).*

Material and methods. *The study included 65 patients with SLE who met the 2012 SLICC classification criteria. GTI, disease activity according to the SLEDAI-2K index and the SLICC damage index (DI) were determined in all patients, and standard laboratory and immunological tests were performed.*

Results and discussion. *Patients were predominantly female (n=56, 86%), median disease duration was 76 [2; 288] months, SLEDAI-2K – 8.8 [0; 26], DI SLICC – 1.0 [0; 5], DI SLICC >0 was found in 28 (43%) patients.*

The median duration of GC therapy during the disease period was 66.0 [0; 288] months, maximum dose of GC – 32.7 [0; 80] mg, median of total GC dose during intravenous administration was 2942 [0; 17 812.5] mg, GTI at the time of enrolment in the study – 19 [0; 37] points. GTI >0 was present in 47 (72%) of 65 patients. GTI correlated with disease duration (r=0.33; p<0.008); maximum dose of oral GCs (r=0.31; p<0.012); duration of GC use (r=0.35; p<0.005); DI SLICC (r=-0.43; p<0.0001). In patients with an average disease duration of more than 3 years, GTI was significantly higher than in patients with a disease duration of 1–3 years (p=0.023).

Conclusion. *An GTI>0 was found in 72% of SLE patients, which increased significantly with disease duration. The GTI value was influenced by the duration of SLE, the duration of GC treatment and the maximum GC dose during the disease period. A statistically significant correlation was found between the GTI and the SLICC DI, allowing the GTI value to be used as an additional component in the assessment of the contribution of GCs to the development of irreversible organ damage in patients with SLE. It is recommended that GTI is assessed in all patients with SLE receiving long-term GC treatment for the purpose of dose adjustment.*

Keywords: *systemic lupus erythematosus; glucocorticoids; irreversible organ damage; glucocorticoid toxicity index.*

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Systemic lupus erythematosus (SLE) is a systemic autoimmune rheumatic disease of unknown etiology, characterized by overproduction of organ-nonspecific autoantibodies to various components of the cell nucleus and the development of immunoinflammatory damage to internal organs [1]. Over the past 50 years, the main drugs for the treatment of this severe disease have been glucocorticoids (GCs). However, along with information about the negative effects of GCs, data are accumulating on their high effectiveness in SLE [2]. D. Apostolopoulos et al. [3] revealed irreversible organ damage in 42% of patients with SLE receiving GCs, while in patients who did not take these drugs, such changes were recorded only in 15% of cases. The most common and severe manifestations of GC toxicity include osteoporosis, osteoporotic fractures, including vertebral compression fractures, osteonecrosis, myopathy, type 2 diabetes mellitus, atherosclerotic vascular disease, arterial hypertension (AH) and cataracts [4]. Many foreign and domestic researchers have shown that high doses of GCs have a significant effect on the rate of increase in the number of lesions along with high disease activity [4–6]. According to other data, an average dose of GC >20 mg/day more than doubles the risk of developing cataracts, osteoporotic fractures and cardiovascular accidents [4–7]. Doses of prednisolone >7.5 mg/day are associated with significant loss of lumbar spine bone mineral density (BMD) and impaired glucose tolerance [4–7]. Taking high doses of GC increases the risk of developing avascular osteonecrosis by 20% [8]. In the Russian cohort, SLE patients with damage index (DI) SLICC (Systemic Lupus International Collaborating Clinics) ≥1 received GCs longer, and at the onset of the disease they were prescribed significantly higher doses of GCs [6]. Increasing cumulative dosage of prednisolone also increased the risk of osteoporotic fractures, cataracts, coronary artery disease, avascular necrosis, and type 2 diabetes mellitus [4]. Prednisolone doses ≤5 mg/day were relatively safe, as was short-term GC pulse therapy. However, the degree of toxicity of low doses of GC requires further study in larger cohorts of patients. Currently, despite the widespread use of immunosuppressants, the emergence of new treatment regimens and the introduction of genetically engineered biological drugs rituximab and belimumab into real clinical practice, more than two thirds of patients never stop taking GCs [2], which over time significantly increases the number of irreversible organ damage.

Physicians still do not have a reliable and simple tool for quantitative assessment of adverse reactions of GCs. Such a tool could be the glucocorticoids toxicity index (GTI), proposed by E.M. Miloslavsky et al. [9] (Table 1). This index includes results from 9 domains: body mass index (BMI); glucose tolerance; arterial hypertension (AH); lipid metabolism; bone mineral density (BMD); steroid myopathy; skin lesions (acne, bruises, hirsutism,

Table 1. GTI [9]

ITG domains	Grade	Most severe toxicities
Body mass index		
Decrease	-8	Significant increase in body mass index
No changes	0	
Moderate increase	21	
Significant increase	36	
Glucose tolerance		
Improvement	-8	Diabetic retinopathy, nephropathy, neuropathy
Without changes	0	
Deterioration	32	
Deterioration despite treatment	44	
AH		
Improvement	-10	Emergency hypertension, posterior reversible encephalopathy syndrome
Without changes	0	
Progression	19	
Progression on treatment	44	
Lipid metabolism		
Decreased blood lipid levels	-9	
No hyperlipidemia	0	
Increased hyperlipidemia	10	
Increased hyperlipidemia despite treatment	30	
Bone mineral density		
Increase	-1	Significant decrease in bone mineral density, osteoporotic fractures
No changes	0	
Decreased bone mineral density	29	
Steroid myopathy		
Absence of steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate or severe steroid myopathy	63	
Skin damage		
No skin damage	0	Severe dermal toxicity
Mild skin damage	8	
Moderate to severe skin damage	26	
Neuropsychiatric disorders		
Absence	0	Psychosis, GC-associated aggression, other severe neuropsychiatric manifestations
Mild	11	
Moderate or more pronounced	74	
Инфекции		
Absence	0	Infections IV and V degrees
Oral/vaginal candidiasis or uncomplicated herpes zoster	19	
Infection III degrees	93	
Endocrine disorders		Adrenal insufficiency
Damage to the gastrointestinal tract		Peptic ulcer
Musculoskeletal lesions		Avascular necrosis, tendon rupture
Eye damage		Central serous retinopathy, increased intraocular pressure, posterior subcapsular cataract
Total score from 36 to 439 points		

atrophy/striae, erosions/ulcerations); neuropsychiatric disorders (sleep disturbance, depression, mania, cognitive impairment) and infections (oral/vaginal candidiasis, or herpes zoster without postherpetic neuralgia, or eye damage, infections requiring hospitalization, intravenous – IV – antibiotics, antifungal or antiviral drugs, herpes zoster, complicated by postherpetic neuralgia or eye damage) [5]. In each of these domains, using mathematical coefficients, pathology is classified as improvement, no change, moderate impairment, or severe impairment. The methodology for determining GTI is presented in more detail in the article by N.Yu. Nikishina et al. [10].

In addition to the quantitative assessment of the general toxicity of GCs, it is recommended to separately indicate a number of the most severe complications caused by GC therapy, but not

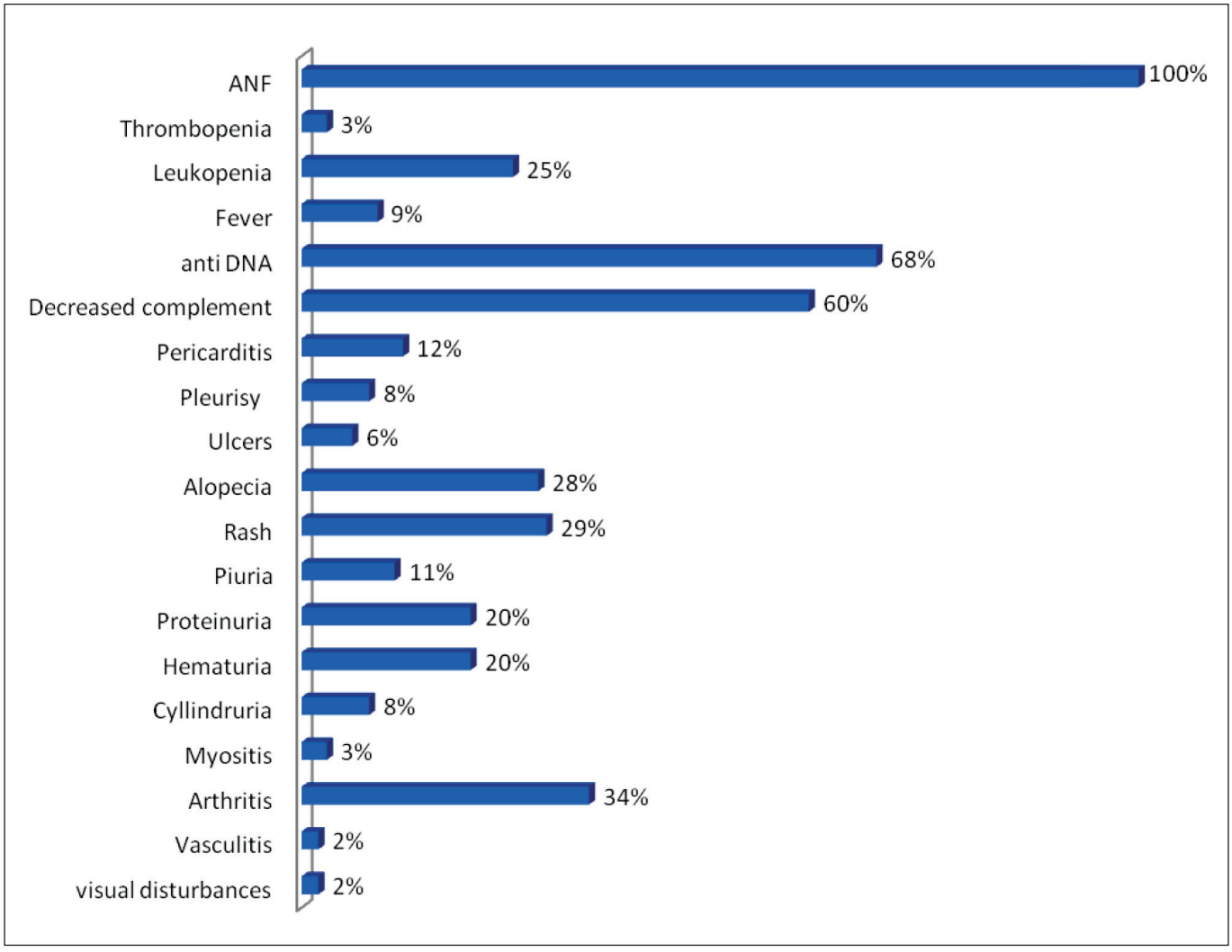

Fig. 1. *Frequency of clinical and immunological signs of SLE, %*

quantified (osteoporotic fractures, osteonecrosis, cataracts, ligament rupture, etc.) [10].

For the immediate assessment of patients with SLE, a cumulative worsening score (CWS) of GCs is used. In the absence of toxicity, the CWS will be equal to 0. When symptoms of GC toxicity are detected in a patient (see Table 1), the GTI CWS is the sum of the corresponding points. With further observation of patients, cases of new toxicity are added to the previously identified GTI CWS value. GTI has been tested and successfully used in studies of patients with asthma and systemic vasculitis [9, 11].

The purpose of the study was to assess the contribution of GCs to the development of irreversible organ damage in patients with SLE using GTI.

Material and methods. The study included 65 patients with SLE who met the 2012 SLICC classification criteria [12], hospitalized at the Federal State Budgetary Institution Research Institute of Rheumatology named after. V.A. Nasonova in 2021–2022. Mandatory conditions for inclusion in the study were the signed informed consent, age over 18 years, a reliable diagnosis of SLE according to the 2012 SLICC classification criteria, the duration of the disease from the onset of the first symptoms to the diagnosis of SLE ≤12 months.

All patients underwent a standard examination recommended by the Association of Rheumatologists of Russia; GTI, DI SLICC and disease activity were determined by the SLEDAI-2K index (systemic lupus erythematosus activity index, modified 2K) [13]. In addition, the duration of GC therapy and the total dose of GCs administered intravenously were calculated for each patient [14].

Statistical analysis was performed using the computer program Statistica 10.0 for Windows (StatSoft Inc., USA). The correspondence of the distribution of indicators to the normal law was checked by the coefficients of asymmetry and kurtosis, and the Kolmogorov-Smirnov criterion. In the case of a normal distribution, the mean (M) and standard deviation (σ) were determined; in case of non-normal distribution, the median and interquartile range (Me [25th; 75th percentile]) were used. The correlation was assessed using Pearson's coefficient. Differences were considered statistically significant at $p<0.05$.

Results. The average age of the patients was 34.0±11.4 years, the median duration of the disease from the appearance of the first signs of the disease to inclusion in the study was 76 [2; 288] months, SLEDAI-2K – 8.8 [0; 26]. The characteristics of the patients are presented in Table. 2.

Table 2. Characteristics of the patients (n=65)

Index	Meaning
Gender, n (%): Men Women	 9 (14) 56 (86)
Age at the time of visit, years, M±σ	34.5±11.4
Age at onset of SLE, years, Me [25; 75 percentiles]	28.5 [11; 57]
Duration of the disease at the time of diagnosis, months, M±σ	8.5±7.7
Duration of the disease at the time of inclusion in the study, months, Me [25; 75 percentiles]	76 [2; 288]
Maximum oral dose of GC during the disease period, mg, Me [25; 75 percentiles]	32.7 [0; 80]
Total dose of GC parenterally during the disease period, mg, Me [25; 75 percentiles]	2942 [0; 17812.5]
SLEDAI-2K, Me [25; 75 percentiles]	8.8 [0; 26]
DI SLICC at the time of visit, Me [25; 75 percentiles]	1.0 [0; 5]
DI SLICC=0, n (%)	37 (57)
DI SLICC 1, n (%)	28 (43)

Clinical manifestations were dominated by skin changes (rashes, alopecia). Acute cutaneous lupus (lupus "butterfly", generalized maculopapular rashes, photosensitivity, generalized erythematous rashes) was detected in 13 (20%) patients, chronic cutaneous lupus – in 2 (3%). Four (6%) patients had signs of both acute and chronic cutaneous lupus. Arthritis and arthralgia occurred in 22 (34%) cases, kidney damage – in 16 (25%). Twelve (19%) patients had lupus nephritis, confirmed by pathomorphological examination of the renal tissue biopsy. Most patients had immunological disorders. Low levels of complement components were detected in 39 (60%) patients, antibodies to DNA (antiDNA) – in 44 (68%). All patients were positive for antinuclear factor (ANF); (Fig. 1).

All patients received GCs; intravenous GCs were prescribed to 42 (65%) patients; the median duration of GC therapy during the disease period was 66.0 [0; 288] months, the maximum dose of GC during the disease period was 32.7 [0; 80] mg, the total dose of intravenously administered GCs during the disease period was 2942 [0; 17812.5] mg.

Aminoquinoline drugs were used by 57 (88%) patients, mycophenolate mofetil – 20 (31%), cyclophosphamide – 21 (32%), azathioprine – 12 (18%), methotrexate – 13 (20%), human immunoglobulin – by 5 (8%) patients.

Nineteen (29%) patients received biological agents, including 16 (25%) receiving rituximab, and 3 (5%) - belimumab. The median DI SLICC [13] at the time of inclusion in the study was 1.0 [0; 5]. DI SLICC >0 was registered in 28 (43%) patients, DI SLICC=0 – in 37 (57%).

The most frequently detected pathologies were irreversible organ damage associated with the use of GCs: cataracts, fractures, avascular necrosis and diabetes mellitus. The leading place among irreversible damage was occupied by cataracts, which were observed in 15 (23%) patients. Irreversible lesions in the form of pulmonary hypertension (n=6.9%), cranial or peripheral neuropathy (n=5.8%), changes in the retina or optic nerve (n=5.8%), thrombophlebitis and aseptic necrosis (n=4.6%) were also relatively common in our patients. Two (3%) patients had a decrease in the glomerular filtration rate <50 ml/min, pulmonary fibrosis, deforming arthritis, osteoporotic fractures, chronic cicatricial alopecia, diabetes mellitus, severe cognitive impairment, convulsive syndrome requiring treatment for more than 6 months, and angina pectoris, prolonged pericarditis (minimum 6 months), stroke, heart attack, proteinuria >3.5 g/day, skin ulceration and tissue loss (eg, phalanges).

The median GTI at the time of inclusion in the study was 19 [0; 37]. GTI >0 was determined in 47 (72%), GTI = 0 in 18 (28%) patients. In 3 of them, the dose of GC was ≤5 mg/day in terms of prednisolone for the entire period of the disease; in 5 patients the duration of the disease was ≤6 months. All these patients had subacute or chronic form of SLE and received GCs for 1–4 months at a dose of <10 mg/day in terms of prednisolone.

In our study, GTI correlated with disease duration (r=0.33), maximum dose of oral GCs (r=0.31), duration of GC treatment (r=0.35), SLICC DI (r=-0.43), p<0.05 in all cases.

To determine the dependence of GTI CWS on the duration of the disease, patients were divided into two groups.

In the 1st group (n=31) the disease duration did not exceed 3 years, in the 2nd group (n=34) it was more than 3 years. In the group with SLE duration of more than 3 years, the average value of GTI was statistically significantly higher (28.2) than in the group with a shorter duration of the disease (16); p<0.023; Fig. 2).

The frequency of signs included in the GTI domains in our patients is presented in Table. 3.

The most common findings were skin lesions (acne, bruises, hirsutism, atrophy/striae), less frequently – increased BMI, hypertension (patients with confirmed lupus nephritis were excluded), and dyslipidemia.

To assess neuropsychiatric manifestations, the Hospital Anxiety and Depression scale (HADS), as well as an oral survey of patients, were used. Neuropsychiatric manifestations (cognitive impairment, decreased memory and attention, mood lability) were diagnosed in 6 (9%) patients, 5 (8%) patients had infectious complications and decreased BMD.

Discussion

According to the treat-to-target concept, "treatment of SLE should be aimed at achieving long-term survival, preventing irreversible organ damage, improving health-related quality of life by

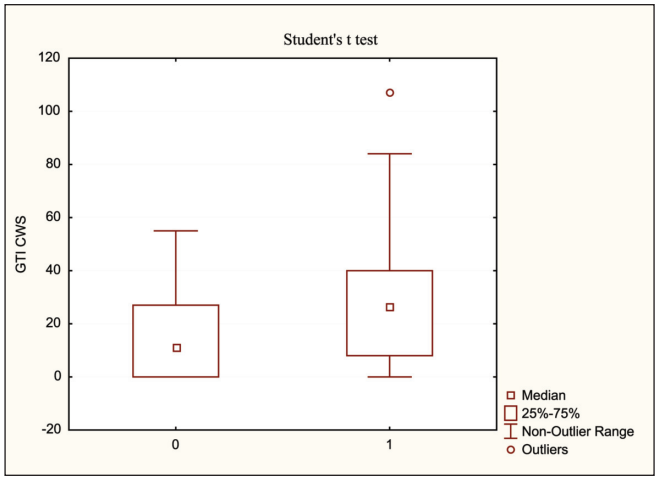

Fig. 2. *GC Cumulative Worsening Score in patients with different duration of SLE*

Table 3. Frequency of features included in the GTI domains (n=65), n (%)

Domain	Meaning
Increased BMI	15 (24)
Decreased glucose tolerance	3 (5)
AH	10 (15)
Dyslipidemia	15 (23)
Steroid myopathy	3 (5)
Decreased bone mineral density	6 (9)
Skin damage	20 (31)
Neuropsychiatric disorders	6 (9)
Infectious complications	5 (8)

controlling disease activity, minimizing the manifestations of concomitant diseases and drug toxicity" [14].

The need for a reliable tool for the assessment of cumulative organ damage led to the creation in 1996 of DI jointly by the SLICC and ACR (American College of Rheumatology) groups [13].

The DI contains items that reflect long-term irreversible damage that the patient has experienced since the diagnosis of SLE. The identified damage should be observed for at least 6 months, with the exception of heart attack and stroke, which are recorded immediately [15]. Lesions included in the DI should be recorded after the diagnosis of SLE, but the evidence of their direct connection with the disease is not required [16]. Therefore, the DI SLICC records an irreversible change in an organ/tissue, but does not prove a cause-and-effect relationship of its development with drug toxicity or disease activity. Some researchers have logically assumed that such an association exists without evidence. In a cohort study by D.D. Gladman et al. [15], the occurrence of lesions in SLE patients was considered as "definitely dependent on GC" (cataracts, avascular necrosis), "probably dependent" (cardiovascular diseases, diabetes mellitus) or "independent" (malignant tumors, lung diseases). A year after the diagnosis of SLE, "definitely GC-dependent" lesions were detected in 58% of patients, while with a longer course of the disease – already in 80%. This study also found that "steroid-independent" lesions are quite common at the early stage of the disease and their occurrence can be explained by the high activity of SLE and the development of autoimmune inflammation of various tissues with subsequent organ damage. Assessing and predicting the toxicity of GCs have previously been difficult due to the lack of a single standardized indicator. Various parameters have been used, such as "duration of use", "cumulative dose" or "average daily dose" [17, 18].

Therefore, the use of GTI, the first standardized indicator of GC toxicity designed to quantify both increase and decrease in toxicity, can help create an evidence base for the involvement of GC in the formation of irreversible organ damage [19].

A recent study by P.J. McDowell et al. [20] included patients (n=101) with severe bronchial asthma who received oral prednisolone at a dose of >10 mg/day for 12 months; the average number of exacerbations per year requiring additional GC prescriptions was 5. These patients showed a high incidence of neuropsychiatric disorders (81.2%), skin changes (79.2%), increased BMI (69.3%) and hypertension (67.3%); GTI averaged 737.

Our work also noted a significant number of cases of increased BMI (24%), skin lesions (31%) and hypertension (15%), although these disorders were significantly less common and the average GTI in the group was much lower.

P.J. McDowell et al. [20] did not indicate the average age of the patients, so we can assume that our patients were younger (36±11.5 years), and this can explain better GTI scores. These authors also traced the correlation between GTI and cumulative doses of prednisolone and the age of patients. The present study also proved the connection between GTI and the duration of GC use and the maximum dose of GC during the period of illness.

A high correlation between cumulative doses of GCs and GTI (p=0.008; 95% confidence interval, CI 1.31–8.05) was demonstrated by L. Floyd et al. [21] in 43 patients with ANCA-associated vasculitis treated with GCs, cyclophosphamide and rituximab. In a recent randomized controlled trial evaluating the efficacy of avacopan 30 mg/day compared with prednisolone in 300 patients with ANCA-associated vasculitis, GTI was used as an additional outcome measure. After 26 weeks of therapy, GTI was 39.7 in the avocopan group and 56.6 in the prednisone group, with a between-group difference of -16.8 (95% CI -25.6 to -8), demonstrating a safer profile of the study drug [22].

Unfortunately, we have not found significant studies assessing GTI in patients with SLE, but we believe that they will definitely appear, since studying the toxicity of GCs in SLE is no less important than in ANCA-associated vasculitis and severe forms of bronchial asthma.

Conclusion

Thus, GTI can be considered a promising tool for determining the toxicity of GCs both in real clinical practice and in randomized clinical trials. Of greatest interest may be its assessment in dynamics, which will be presented in our next publication.

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