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MEASURES IN ASSESSMENT OF PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS: AN EXPERIENCE OF RETROSPECTIVE OBSERVATIONAL STUDY

© E.M. Kuchinskaya, V.G. Chasnyk, M.M. Kostik

St. Petersburg State Pediatric Medical University, Ministry of Healthcare of the Russian Federation, Russia

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Systemic lupus erythematosus in children (juvenile-onset SLE, jSLE) is a multisystemic disease with an unpredictable course and a more severe phenotype compared to adults. The patterns of jSLE are extremely heterogeneous, so an enrollment to controlled studies may be rather complicated. Due to this problem and some additional ones, there are no standards for treatment of jSLE yet. The attending physician is fully responsible for the induction and maintenance therapeutical options including durability and aggressiveness. ***Objectives:*** finding of jSLE individual course's features prognostically connected with the disease outcome. ***Methods:*** 45 children admitted to the SPbGPMU hospital with the systemic lupus erythematosus diagnosed at the age of 4-17 years were enrolled in this retrospective study. Primary SLE manifestations, the activity of disease according to SELENA-SLEDAI and ECLAM scales during initial treatment period and flares after it, the fact of remission achievement in 6 months were evaluated in each patient. ***Results:*** a few organ involvements were considered to be connected with outcome's characteristics, for example lupus nephritis and early disease oncet are unfavorable predictive factors. The positive connection of favorable outcome with cyclophosphamide, intravenous methylprednisolone and mycophenolate mofetil was found; the negative connection between initial disease activity and flares after induction treatment was also noticed. ***Conclusion:*** the patient with initially high disease activity treated aggressively with high cumulative doses of cyclophosphamide, intravenous methylprednisolone and mycophenolate mofetil has more chances of the favorable outcome (the achievement of remission without further flares).

Keywords: systemic lupus erythematosus; systemic lupus erythematosus in children; SLE; SLEDAI; ECLAM; SLE treatment; cyclophosphamide; methylprednisolone; mycophenolate mofetil.

СИСТЕМНАЯ КРАСНАЯ ВОЛЧАНКА У ДЕТЕЙ: ПРИМЕНЕНИЕ ФОРМАЛИЗОВАННЫХ МЕТОДОВ ОПИСАНИЯ ТЕЧЕНИЯ И ИСХОДА ЗАБОЛЕВАНИЯ В РЕТРОСПЕКТИВНОМ ИССЛЕДОВАНИИ

© Е.М. Кучинская, В.Г. Часнык, М.М. Костик

ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России

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Системная красная волчанка (СКВ), дебютировавшая в детском возрасте, — мультиорганное заболевание с более тяжелым, чем у взрослых, течением. Индивидуальные сценарии заболевания исключительно разнообразны, вследствие чего подбор групп пациентов в контролируемые исследования затруднен и стандарты лечения не выработаны. Выбор препаратов для начальной и поддерживающей терапии с учетом степени агрессивности лечения, его длительности является решением лечащего врача. ***Цель исследования*** — определение характеристик индивидуального сценария СКВ у детей, достоверно влияющих на исход заболевания. ***Материалы и методы.*** Настоящее ретроспективное исследование включает 45 пациентов с СКВ с дебютом заболевания в возрасте от 4 до 17 лет, находившихся на стационарном лечении в СПбГПМУ. Для каждого пациента были описаны следующие характеристики: органные вовлечения на момент начала терапии, активность заболевания (согласно индексам SELENA-SLEDAI и ECLAM) на момент начала терапии и через 6 месяцев, характер начальной терапии; достижение нескольких видов ремиссии через 6 месяцев, обострения в периоде после индукции. ***Результаты.*** В данном исследовании связи органных вовлечений с характеристиками исхода немногочисленны, наиболее неблагоприятными прогностическими признаками являются поражение почек и ранний возраст дебюта. Среди лекарственных препаратов достоверные положительные связи с благоприятным исходом установлены для циклофосфамида, внутривенного метилпреднизолона и мофетила микофенолата. Обнаружена также обратная связь

исходной активности СКВ с наличием обострений после индукции. ***Заключение.*** Больше шансов на благоприятный исход (достижение ремиссии и отсутствие обострений после нее) имеет пациент с изначально более высокой степенью активности СКВ, получивший агрессивную начальную терапию (с высокими кумулятивными дозами циклофосфамида, внутривенного метилпреднизолона, использованием мофетила микофенолата).

Ключевые слова: системная красная волчанка; системная красная волчанка у детей; СКВ; SLEDAI; ECLAM; лечение СКВ; циклофосфамид.

INTRODUCTION

Approximately 10–20% of systemic lupus erythematosus (SLE) cases occur during childhood. Despite differences in design, cohort studies performed in the past few decades suggested that the course of SLE initiated in childhood is associated with greater severity, higher rate of disease activity and degree of organ damage compared with the course of SLE manifested in older age [1–3].

There is a significant difference in the frequency of organ involvement and clinical manifestations between adults and children of different age groups. Moreover, there are differences in the use of various drugs suppressing the disease activity. In general, pediatric patients receive more aggressive treatment [6]. Currently, there is a lack of established recommndations for the treatment of SLE in children.

The number of randomized trials with qualitative design, investigating SLE in children, is limited. Hence, currently the main source of data on SLE is research conducted on adult populations. In addition, the wide variability of the course of SLE makes it difficult to study homogeneous patient groups. Therefore, the results obtained and the treatment recommendations derived from those findings are specific to the involvement of a particular organ (e. g., treatment of lupus nephritis or central nervous system lesion) or complications of the disease (macrophage activation syndrome) [3]. The choice of therapy takes into account a variety of individual factors such as organ involvement, age, heredity, aggressiveness of the disease, as well as the prognosis and risk of exacerbation in remission, and remains the prerogative of the treating physician.

The objective of this study was to determine the characteristics of an individual scenario of SLE in a deliberately selected heterogeneous group of pediatric patients.

MATERIALS AND METHODS

A retrospective study including 45 patients with various forms of SLE and onset of disease ≤18 years of age. The patients were hospitalized in the Pediatric Department No. 3 of the Federal State Budgetary Educational Institution of Higher Education St. Petersburg State Pediatric Medical University, Ministry of Health of the Russian Federation. Diagnosis of SLE was established based on the American College of Rheumatology (ACR) 1997 criteria. For each patient, organ involvement at the time of disease onset, and laboratory (including immunological) characteristics at the time of therapy initiation were determined. The concept of initial therapy (remission induction), traditionally recommended for the treatment of lupus nephritis, was introduced to limit the time frame. The average duration of induction therapy was 6 months [5].

Indices such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) as modified in the Safety of Estrogens in Lupus National Assessment (SELENA) SLEDAI study and the European Consensus Lupus Activity Measurement (ECLAM) were used to assess the activity of the disease. Evaluation was conducted at the time of initiation and termination of induction therapy.

The therapy involved cumulative doses of cyclophosphamide and intravenous methylprednisolone (pulse therapy) per 1 m^2 of body surface and 1 kg of body weight, respectively; doses of intravenous immunoglobulin and rituximab; and use of other agents controlling disease activity such as mycophenolate mofetil, oral glucocorticosteroids, azathioprine, and hydroxychloroquine.

Achievement of remission based on the SLEDAI (clinical and laboratory), clinical remission based on the ECLAM index, minimal clinically significant improvement in activity scores (-7 points for SELENA SLEDAI and -3 points for ECLAM) [9], and the presence of exacerbations of the disease after the initial treatment period, according to the SELENA flare index (SFI) during the observation period, were used as indicators of treatment efficacy.

STATISTICAL METHODS

Statistical analysis was performed using the statistical software packages Statistica 10.0 and Microsoft Excel. The Spearman rank correlation coefficient was used to assess correlations between clinical and laboratory findings as well as with the indices of treatment efficacy. The reliability of the differences between independent groups formed according to the presence of correlations was verified using the non-parametric Mann–Whitney *U*-test. For categorical quantities, the two-tailed exact Fisher's test was used.

RESULTS

The majority of patients enrolled in this study were females (84.4%). The median age of disease onset was 13 years (range: 4–17 years). The most frequent organ involvement was skin and mucous membrane lesion (71.1%) and arthritis (55.6%), while the most frequent laboratory finding (after antinuclear factor and antibodies to double-stranded DNA) was anemia (51.1%).

Most patients (80%) received oral corticosteroids during initial therapy. The efficacy of treatment was evaluated 6 months (on average) after treatment initiation. One patient expired during the first month of observation due to disease severity.

As a result of treatment, remission was achieved in 12 to 21 patients (evaluated according to two different scales of activity). Disease exacerbations were noted after the initial therapy period (taking into account the entire observation period) in 13 patients (28.9%). The detailed demographic characteristics of the study population are provided in Table 1.

The Spearman rank correlation coefficient was used to assess the relationship between indicators within the study group. All characteristics correlated to the efficacy of therapy are presented in Table 2. Patients were classified into groups based on these parameters and the significance of the differences observed was determined using analysis of variance (Tables 3 and 4). Mutual correlations of various remission indicators were self-evident and were not tested further.

According to the results of the analysis, a significantly unfavorable prognostic factor for achieving two of the three types of remission (clinical remission based on the SLEDAI and clinical remission based on the ECLAM) is renal damage. Other prognostically signifi-

Table 1

Demographic characteristics of patients included in the study

Sign		*n* (%)	Finding		*n* (%)
Total		45 (100)	Laboratory characteristics	Antinuclear antibody	44 (97.8)
Female gender		38 (84.4)		Antibodies to double-stranded DNA	36 (80)
Clinical manifestations	Skin/mucosa	32 (71.1)		Antibodies to SS-A/SS-B	9 (20)
	Alopecia	8 (17.8)		Anti-Sm antibodies	12 (26.7)
	Arthritis	25 (55.6)		Antibodies to RiboP	3 (6.7)
	Serositis	8 (17.8)		Antibodies to nucleosomes	15 (33.3)
	Nephritis	13 (28.9)		Antibodies to histones	6 (13.3)
	Lung lesions	8 (17.8)		Antibodies to cardiolipin and β_2-glycoprotein	15 (33.3)
	Myocarditis	10 (22.2)		Rheumatoid factor	8 (17.8)
	Enlarged liver/spleen	10 (22.2)		Hypocomplementemia	11 (24.4)
	Myositis	4 (8.9)		Anemia	23 (51.1)
	CNS lesions	16 (35.6)		Thrombocytopenia	10 (22.2)
	Lymphadenopathy	8 (17.8)		Leukocytopenia	15 (33.3)
	GI lesions	6 (13.3)		Lymphopenia	4 (8.9)
	Raynaud syndrome	6 (13.3)	Therapy:		
	Skin vasculitis	11 (24.4)	• Pulse therapy with methylprednisolone		29 (64.4)
	Thrombosis	7 (15.6)	• Cyclophosphamide		24 (53.3)
	Sjogren's syndrome	6 (13.3)	• Hydroxychloroquine		27 (60)
	Fever	26 (57.8)	• Mycophenolate mofetil		14 (31.1)
			• Azathioprine		6 (13.3)
			• Methotrexate		7 (15.6)
			• Oral corticosteroids		36 (80)
			• Rituximab		9 (20)
Outcomes:			Onset age, years		Med (25–75%)
• Clinical and laboratory remission based on the SLEDAI		12 (26.7)	• From disease onset to treatment initiation, months		13.0 (10.0–14.0)
• Clinical remission based on the SLEDAI		19 (42.2)	• From treatment initiation to the time of evaluation		5.0 (3.0–12.0)
• Clinical remission based on the ECLAM		21 (46.7)	• Observation after termination of initial therapy, month(s):		
• Significant change in score based on the SLEDAI		19 (42.2)	a) Prior to the first exacerbation		6.0 (5.99–6.0)
• Significant change in score based on the ECLAM		24 (53.3)	b) Duration of observation in the absence of exacerbations.		7.0 (4.0–20.0)
• Exacerbation after initial therapy		13 (28.9)			18.0 (5.0–28.5)
• Death during initial therapy		1 (2.2)			

Table 2

Coefficient of Spearman rank correlation for indices of efficiency of initial therapy (n = 45). The values noted are statistically significant ($p < 0.05$)

Indices	Exacerbations after induction	Clinical remission based on the SLEDAI	Clinical and laboratory remission based on the SLEDAI	Clinical remission based on the ECLAM	Significant improvement based on the SLEDAI	Significant improvement based on the ECLAM
Onset age	–0.26	*0.30*	*0.34*	*0.31*	0.25	*0.37*
Skin lesion	–0.03	–0.25	*–0.39*	0.01	0.15	–0.01
Serositis (pleurisy/pericarditis)	–0.04	–0.16	–0.02	–0.09	*0.31*	0.09
Nephritis	0.03	*–0.35*	–0.27	*–0.40*	0.05	0.10
Hepato/splenomegaly	*0.37*	–0.13	–0.20	–0.18	0.08	–0.04
Anti-Sm- antibodies	–0.05	0.20	0.09	*0.34*	–0.11	0.16
Cutaneous vasculitis	*0.32*	0.04	–0.11	–0.01	0.04	–0.19
Central nervous system lesion	–0.17	0.21	0.18	0.05	*0.30*	*0.32*
Anemia	–0.26	*0.30*	0.29	0.11	0.21	0.24
Lymphopenia	–0.03	0.05	–0.01	0.02	*0.37*	0.14
Pulse therapy with methylprednisolone	–0.24	0.26	0.24	0.14	*0.35*	*0.42*
Cumulative dose of pulse therapy with methylprednisolone	–0.22	*0.32*	0.29	0.19	*0.39*	*0.42*
Cyclophosphamide (intravenous)	*–0.39*	*0.35*	*0.36*	0.25	*0.53*	*0.38*
Cumulative dose of cyclophosphamide	*–0.40*	0.28	*0.33*	0.21	*0.56*	*0.33*
Mycophenolate mofetil	*–0.30*	*0.33*	0.21	0.11	*0.36*	*0.41*
Prednisolone (*per os*)	–0.05	*0.31*	0.18	0.24	0.20	0.20
SLEDAI score before induction	*–0.33*	–0.06	–0.03	0.02	*0.66*	*0.42*
ECLAM score before induction	–0.29	0.09	0.18	0.09	*0.54*	*0.63*
Clinical remission based on the ECLAM	*–0.40*	*0.73*	*0.44*	1.00	0.28	*0.52*
Significant improvement based on the SLEDAI	*–0.45*	0.27	*0.30*	0.28	1.00	*0.53*
Significant improvement based on the ECLAM	*–0.48*	*0.44*	*0.36*	*0.52*	*0.53*	1.00

cant factors at disease onset are sparse and noted sporadically. The presence of hepato- or splenomegaly during disease onset is associated with exacerbations after the initial therapy period. Lymphopenia, the presence of anti-Sm antibodies, and fever were shown to be prognostically favorable, whereas skin lesions were prognostically unfavorable.

The groups of patients who achieved clinical and laboratory remission (SLEDAI and ECLAM) had an onset at a significantly older age (for clinical remission based on the SLEDAI the correlation does not reach statistical significance). This may be due to both the "nonstandard" course of SLE in young children and the longer observation period of up to 18 years.

The results of the analysis showed a statistically significant negative association between exacerbations after induction and a baseline disease activity score on the SELENA SLEDAI scale. Further analysis revealed that a clinically significant improvement on the SELENA SLEDAI and ECLAM scales is also associated with initially higher activity scores but here the calculation technique plays a role as the initially low score does not change as much as the high score. In patients with induced clinical remission based on the ECLAM, exacerbations were significantly less frequent.

Those drugs which efficacy of therapy is associated (in different combinations and with varying degrees of significance) only with mycophenolate mofetil, cyclophosphamide and intravenous methylprednisolone (for the last two drugs, the association can be traced with both the fact of use and the cumulative dose). Other

Table 3

Comparisons of independent groups: *U*-test (for quantitative variables). The values noted are statistically significant ($p < 0,05$)

Indices	Presence of exacerbations after induction		Absence of exacerbations after induction		*p*
	n	M_e(IQR)	*n*	M_e(IQR)	
Cumulative dose of cyclophosphamide	13	0.0 (0.0–0.0)	32	2471.0 (0.0–4066.5)	*0.009*
SLEDAI score before induction	13	6.0 (4.0–13.0)	32	14.0 (7.0–18.0)	*0.03*
	Clinical remission based on the SLEDAI is achieved		Clinical remission based on the SLEDAI is not achieved		*p*
	n	M_e(IQR)	*n*	M_e(IQR)	
Age of disease onset	19	13.0 (10.0–15.0)	26	12.0 (9.0–13.0)	0.05
Cumulative dose of pulse therapy with methylprednisolone	19	75.0 (30.0–166.0)	26	14.5 (0.0–42.0)	*0.03*
	Clinical and laboratory remission based on the SLEDAI is achieved		Clinical and laboratory remission based on the SLEDAI is not achieved		*p*
	n	M_e(IQR)	*n*	M_e(IQR)	
Age of disease onset	12	14.0 (12.5–15.0)	33	12.0 (10.0–13.0)	*0.02*
Cumulative dose of cyclophosphamide	12	2967.5 (1000.0–4466.5)	33	0.0 (0.0–3000.0)	*0.03*
	Clinical remission based on the ECLAM is achieved		Clinical remission based on the ECLAM is not achieved		*p*
	n	M_e(IQR)	*n*	M_e(IQR)	
Age of disease onset	21	13.0 (10.0–15.0)	24	12.0 (9.0–13.0)	*0.04*
	Significant improvement based on the SLEDAI		Minor improvement/no improvement based on the SLEDAI		*p*
	n	M_e(IQR)	*n*	M_e(IQR)	
Cumulative dose of pulse therapy with methyl-prednisolone	19	75.0 (20.0–188.0)	26	12.0 (0.0–51.0)	*0.01*
Cumulative dose of cyclophosphamide	19	3175.0 (1660.0–4666.0)	26	0.0 (0.0–400.0)	*0.0002*
SLEDAI score before induction	19	17.0 (14.0–22.0)	26	6.0 (4.0–8.0)	*0.00001*
ECLAM score before induction	19	6.0 (4.0–6.0)	26	2.5 (2.0–4.0)	*0.0003*
	Significant improvement based on the ECLAM		Minor improvement/no improvement based on the ECLAM		*p*
	n	M_e(IQR)	*n*	M_e(IQR)	
Age of disease onset	24	13.0 (11.0–15.0)	21	12.0 (9.0–13.0)	*0.02*
Cumulative dose of pulse therapy with methylprednisolone	24	72.0 (25.0–178.0)	21	0.0 (0.0–36.0)	*0.005*
Cumulative dose of cyclophosphamide	24	2471.0 (0.0–4066.0)	21	0.0 (0.0–400.0)	*0.03*
SLEDAI score before induction	24	15.0 (8.0–18.0)	21	6.0 (4.0–14.0)	*0.006*
ECLAM score before induction	24	5.5 (4.0–6.0)	21	2.0 (2.0–4.0)	*0.00003*

Table 4

Comparisons of independent groups: two-tailed exact Fisher's test (for qualitative variables). The values noted are statistically significant ($p < 0,05$)

Indices		Exacerbations after induction		
		Absence of exacerbations	Presence of exacerbations	Fisher's exact p, two-tailed
Hepato/splenomegaly	No	28	7	*0.02*
	Yes	4	6	
Cutaneous vasculitis	No	27	7	0.05
	Yes	5	6	
Cyclophosphamide (intravenous)	No	11	10	*0.02*
	Yes	21	3	
Mycophenolate mofetil	No	19	12	*0.04*
	Yes	13	1	
Clinical remission based on the ECLAM	No	13	11	*0.01*
	Yes	19	2	
Significant improvement in SLEDAI score	No	14	12	*0.003*
	Yes	18	1	
Significant improvement in ECLAM score	No	10	11	*0.002*
	Yes	22	2	
		Clinical remission based on the SLEDAI		
		Not achieved	Achieved	Fisher's exact p, two-tailed
Nephritis	No	15	11	*0.02*
	Yes	17	2	
Anemia	No	16	6	0.07
	Yes	10	13	
Cyclophosphamide (intravenous)	No	16	5	*0.03*
	Yes	10	14	
Mycophenolate mofetil	No	20	11	0.2
	Yes	6	8	
Prednisolone (*per os*)	No	8	1	0.06
	Yes	18	18	
		Clinical and laboratory remission based on the SLEDAI		
		Not achieved	Achieved	Fisher's exact p, two-tailed
Skin lesion	No	6	7	*0.02*
	Yes	27	5	
Cyclophosphamide (intravenous)	No	19	2	*0.02*
	Yes	14	10	
		Clinical remission based on the ECLAM		
		Not achieved	Achieved	Fisher's exact p, two-tailed
Nephritis	No	13	19	*0.01*
	Yes	11	2	
Anti-Sm-antibodies	No	21	12	*0,04*
	Yes	3	9	

Continuation of table 4

Indices		Exacerbations after induction		
		Absence of exacerbations	Presence of exacerbations	Fisher's exact p, two-tailed
		Improvement on SLEDAI		
		Minor/absent	Significant	Fisher's exact p, two-tailed
Serositis (pleurisy/pericarditis)	No	24	13	0.05
	Yes	2	6	
Central nervous system lesion	No	20	9	0.06
	Yes	6	10	
Lymphopenia	No	26	15	*0.03*
	Yes	0	4	
Pulse therapy with methylprednisolone	No	13	3	*0.03*
	Yes	13	16	
Cyclophosphamide (intravenous)	No	18	3	*0.001*
	Yes	8	16	
Mycophenolate mofetil	No	21	10	0.06
		5	9	
		Improvement based on the ECLAM		
		Minor/absent	Significant	Fisher's exact p, two-tailed
Central nervous system lesion	No	17	12	0.06
	Yes	4	12	
Pulse therapy with methylprednisolone	No	12	4	*0.006*
	Yes	9	20	
Cyclophosphamide (intravenous)	No	14	7	*0.02*
	Yes	7	17	
Mycophenolate mofetil	No	18	13	*0.03*
	Yes	3	11	

drugs did not show significant correlations with therapy efficacy indicators.

The aim of SLE therapy is to achieve remission or improvement based on the SLEDAI scale. Thus, a cumulative dose of cyclophosphamide plays a crucial role, whereas the number of methylprednisolone pulses and the use of mycophenolate mofetil appear to be less important. A criterion of therapy efficacy is the absence of disease exacerbations. Therefore, a child with initially high disease activity and clinical remission based on the ECLAM scale, receiving aggressive initial therapy with cyclophosphamide, may have a higher chance of a favorable outcome.

DISCUSSION

The heterogeneity of the clinical and laboratory manifestations of SLE limits the application of the "treat-to-target" principle i. e., treatment until the objective is reached. This principle has been useful for the management of other systemic diseases such as rheumatoid arthritis. According to the recommendations of the international working group, the aim of SLE therapy in adults is clinical remission or, if remission is not achievable, the minimum possible activity of the disease (estimated using a validated index or organ-specific markers such as the degree of proteinuria) [10]. Currently, a single definition of remission for SLE is not available. According to the recommendations of the Definitions Of Remission In SLE (DORIS) group, remission is a long-term condition (without specific time limits) [11]. Validated clinical indices are used to define remission (SLEDAI = 0; BILAG 2004 – only values of D or E; ECLAM = 0). The exact role of positive serology of SLE in the definition of remission (hypocomplementemia and antibodies to double-stranded DNA for the SLEDAI, and hypocomplementemia for ECLAM) has not been elucidated and requires further investigation.

In the present study, two variants of remission based on the SLEDAI were used, such as without serology (clinical remission) and clinical and laboratory remission (SLEDAI = 0). In remission based on the ECLAM,

hypocomplementemia was not considered. Since the "lowest possible achievable" value of indices was not determined, minimal clinically significant changes in the index were used [9].

The absence of exacerbations is also considered by the international group as the target of SLE therapy. Although the timing and volume of maintenance therapy for lupus nephritis [7] are defined in the recommendations, these parameters remain at the discretion of the treating physician for the involvement of other organs. Processing data on maintenance therapy may be difficult due to concomitant administration of drugs, timing, doses, and frequent compliance disorders). Therefore, the outcomes of initial therapy were considered as predictors of disease exacerbation.

At present, there is a lack of evidence from controlled clinical studies supporting the advantages of the "treat-to-target" approach. The implementation of this strategy is hampered by the variability of the course of disease, as well as by the limited armamentarium of medications available to the treating rheumatologist [8].

The high toxicity of the most effective agents (cytostatic agents and parenteral methylprednisolone) is associated with irreversible organ damage, which is difficult to control in children and adolescents (usually due to the transition to an adult health care institution network). Aggressive therapy without taking into account the individual characteristics of the course of SLE in a child may be attractive in terms of achieving remission and control of exacerbations. However, this approach may have severe and unpredictable consequences in the long term. Therefore, further research into reliable organ-specific markers of disease activity, as well as the development of individualized therapy using modern genetic engineering drugs is warranted.

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◆ Information about the authors

Ekaterina M. Kuchinskaya — Postgraduate Student, Department of Hospital Pediatrics. St. Petersburg State Pediatric Medical University, St. Petersburg, Russia. E-mail: kuchinskaya.link@gmail.com.

◆ Информация об авторах

Екатерина Михайловна Кучинская — аспирант, кафедра госпитальной педиатрии. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: kuchinskaya.link@gmail.com.

◆ Information about the authors

Vyacheslav G. Chasnyk — MD, PhD, Dr Med Sci, Professor, Head, Department of Hospital Pediatrics. St. Petersburg State Pediatric Medical University, St. Petersburg, Russia. E-mail: chasnyk@list.ru.

Mikhail M. Kostik — MD, PhD, Associate Professor, Department of Hospital Pediatrics. St. Petersburg State Pediatric Medical University, St. Petersburg, Russia. E-mail: kost-mikhail@yandex.ru.

◆ Информация об авторах

Вячеслав Григорьевич Часнык — д-р мед. наук, профессор, заведующий, кафедра госпитальной педиатрии. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: chasnyk@list.ru.

Михаил Михайлович Костик — канд. мед. наук, доцент, кафедра госпитальной педиатрии. ФГБОУ ВО «Санкт-Петербургский государственный педиатрический медицинский университет» Минздрава России, Санкт-Петербург. E-mail: kost-mikhail@yandex.ru.