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Retrospective analysis of infections prevalence in patients with progressive systemic sclerosis treated with cyclophosphamide

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ABSTRACT

Aim. Assessment of infections prevalence rate, type and severity in patients diagnosed with progressive systemic sclerosis (PSS), treated with cyclophosphamide (CTX), during 12 months of observations.
Material and methods. A retrospective analysis of mild, moderate and severe infections in 17 women with a mean age of 58.8 ± 10.0, based on an interview, physical examination, additional tests, and available medical records.
Results. 46 various infections were diagnosed in the analysed group of patients. 32 (69.6%) infections involved the respiratory system, and 14 (30.4%) infections concerned the urinary tract. The average frequency per one patient was 2.7 ± 3.5 (median: 2) events during 12 months of observations. The majority of infections, 60.9 % (n = 28), were mild ones of slight intensity, and 37.0% (n = 17) were moderate ones. Only one person (2.2% of all infections) had a severe infection requiring hospitalisation.
Conclusions. In the studied group the infection prevalence rate was comparable to that in a healthy population. The majority of infections were mild and involved the respiratory system. Basis of conducted analysis 12 months intravenous administration of CTX is not a factor significantly increasing a risk of severe infections in the studied group of patients. In PSS patients CTX pulse therapy is relatively safe, as it does not cause severe infections requiring hospitalisation.

Keywords: infections, progressive systemic sclerosis, cyclophosphamide treatment.

Introduction

Progressive systemic sclerosis (PSS) is one of the most severe systemic diseases of connective tissue. Causal treatment of PSS is yet unknown. Currently used therapies only aim at inhibiting the inflammatory process and progressive multi-organ fibrosis. One of the treatment methods known for years is immunosuppression with cyclophosphamide (CTX). This medicine belongs to standard cytostatic agents used in treatment of autoimmune diseases and cancers. The anti-inflammatory mechanism underlying the effect of CTX metabolites is based on alkylation of deoxyribonucleic acid (DNA) in mature T- and B-cells (and, to a smaller extent, bone marrow precursor cells), resulting in their damage and death [1, 2]. In PSS cyclophosphamide inhibits progression of interstitial lesions in lungs and has an advantageous influence on skin sclerosis remission [2–4]. It also improves respiratory system efficiency measured as forced vital capacity (FVC) [3, 4, 6], total lung capacity (TLC) [4] and *diffusing* capacity of the lungs for carbon monoxide (DLCO) [7, 8]. Therefore CTX treatment improves quality of patients' life [3]. Recent recommendations of The European League Against Rheumatism (EULAR), published in 2009, recommend considering use of CTX for early lung lesions, scleroderma-related interstitial lung disease (SSc-ILD), as remission-inducing therapy [10]. Despite proven

efficacy and safety of CTX, this treatment may involve some adverse effects, including infections [3, 10]. In studies on using CTX in patients with PSS and other autoimmune diseases (vasculitis, systemic lupus erythematosus and others) it was observed that benefits of this therapy exceed a related risk of possible infections [11]. Infection severity depends mainly on the administration route and a cumulative dose of CTX. High-dose intravenous CTX therapy (50 mg/kg/d for 4 consecutive days) not related to a stem cells transplant is mainly applied in treatment of aplastic anaemia [2, 9]. This treatment was also attempted in PSS patients in the past, and it resulted in skin lesions remission and improvement in quality of life [9, 12]. However, this regimen and dosing is associated with a significantly higher number of complications and sometimes required numerous preventive activities, including administration of the *granulocyte* colony-stimulating factor (G-*CSF*), mesna, antibiotic therapy, or antifungal treatment. Therefore, currently this regimen is not recommended for PSS treatment. Oral CTX administration at 1–2 mg/kg/daily results in an even distribution of the dose, usually not requiring prevention of severe infections; however, it is still related to a high cumulative dose, increasing the rate of adverse effects [3, 6]. However, this dose can be significantly reduced and yet as effective, when CTX is administered intravenously in intravenous pulse therapy at low single doses. Using results of a multicentre, prospective, randomised, double-blind study, it is recommended to replace the oral drug with CTX at a dose of 600 mg/m², intravenously, once a month for six months [5]. There are numerous examples in the literature confirming effectiveness of low-dose intravenous CTX therapy in PSS patients [11, 13, 14, 15]. This treatment regimen may reduce a risk of various adverse effects, including infections, during long-term therapy.

Material and methods

All 17 women who were included in this study fulfilled the PSS classification criteria of The American College of Rheumatology / The European League Against Rheumatism (ACR/EULAR 2013) [15]. Selected population of patients, received CTX intravenously in a pulse therapy during the mean time of 12.0 ± 4.0 months. The mean age in the studied group was 58.8 ± 10.0 years (median: 60 years), and the mean disease duration from the moment of its diagnosis was 53.7 ± 51.1 months (median: 36 months). The patients were treated with CTX at a dose of 400–800 mg, applied as a single dose every 1–3 months. In the studied group, the mean CTX cumulative dose was 9870.6 mg ± 6724.2 mg (median: 8600 mg), ranging from 2000–25600 mg (**Table 1**).

Table 1. Characteristic of patients with PSS

N	Age (years)	DD (months)	CTX (mg)	ANA[1]	Immunological profile[2]			Pulmonary changes[3]	PAH[4]
					Scl 70	CENB	PM-Scl		
1.	64	108	22800	positive	+++	–	–	(+++)	yes
2.	49	84	25600	positive	+++	–	–	(+++)	yes
3.	54	12	4200	positive	+++	–	–	negative	–
4.	65	36	10800	positive	+++	–	–	(+)	–
5.	61	132	10000	positive	–	–	–	(+++)	yes
6.	57	60	10200	positive	+	+++	–	(+++)	–
7.	52	193	5200	positive	–	–	–	(++)	–
8.	47	24	11000	positive	+	–	–	(++)	yes
9.	62	24	7000	positive	–	–	–	(+++)	yes
10.	62	12	6000	positive	+++	–	–	(++)	–
11.	36	24	9000	positive	–	+	+++	(++)	yes
12.	66	12	6000	positive	–	–	–	(+)	–
13.	60	60	8600	positive	–	+++	–	(+++)	–
14.	59	12	4600	positive	–	–	–	(+++)	–
15.	76	36	5000	positive	+	–	–	(+++)	yes
16.	54	12	2000	–	–	–	–	(+++)	–
17.	76	72	19800	positive	+++	–	–	(+++)	–

1. Detected by the immunoenzymatic test ANA Screen; laboratory standard: < 40 U/ml
2. + – weakly positive result; ++ – positive result; +++ – strong positive result
3. On a basis of computed tomography; (+) – minimal, preliminary changes, basal fibrosis; (++) – interstitial changes; (+++) – ground-glass opacities, honeycombing
4. Pulmonary arterial hypertension is probable: RVSP > 30mmHg in the transthoracic echocardiography

N – the number of patients; DD – diseases duration; ANA – antinuclear antibodies; Scl 70 – anti- topomisomerase I antibodies; CENB – anti-centromere protein B antibodies; PM-Scl – anti- polymyositis/scleroderma antibodies; PAH – pulmonary arterial hypertension

Table 2. Classifications of severity and type of the studied infections in patients with PSS

Type of infection	Treatment of infection	Localization of infection
Mild infection	Infection of mild intensity treated without antibiotics, antiviral or antifungal medications	the upper respiratory tract
		the urinary tract
		skin and/or subcutaneous tissue
Moderate infection	Infection treated with antibiotics, antiviral or antifungal medications in the ambulatory care, without complications, with rapid regression of the symptoms	the upper respiratory tract
		the lower respiratory tract
		the urinary tract
		skin and/or subcutaneous tissue
Severe infection	Infection requiring hospitalisation, treated by intravenous drugs or recurrent, chronic, resistant to standard treatment	the upper respiratory tract
		the lower respiratory tract
		the urinary tract
		skin and/or subcutaneous tissue

Table 3. Infections prevalence rate, type and severity in studied group of patients with Progressive Systemic Sclerosis

N	Mild infection			Moderate infection				Severe infection			
	URT	UT	S/SCT	URT	LRT	UT	S/SCT	URT	LRT	UT	S/SCT
1.	–	–	–	–	–	–	–	–	–	–	–
2.	1	–	–	1	–	–	–	–	–	–	–
3.	–	1	–	–	–	1	–	–	–	–	–
4.	2	–	–	–	–	–	–	–	–	–	–
5.	–	–	–	1	–	–	–	–	–	–	–
6.	–	–	–	3	–	–	–	–	–	–	–
7.	5	3	–	–	2	–	–	–	1	–	–
8.	2	–	–	–	–	–	–	–	–	–	–
9.	–	1	–	–	–	–	–	–	–	–	–
10.	–	–	–	–	–	–	–	–	–	–	–
11.	4	–	–	–	–	–	–	–	–	–	–
12.	2	–	–	–	–	–	–	–	–	–	–
13.	–	–	–	–	1	–	–	–	–	–	–
14.	–	–	–	1	–	–	–	–	–	–	–
15.	2	5	–	3	1	1	–	–	–	–	–
16.	–	–	–	–	–	–	–	–	–	–	–
17.	–	–	–	–	–	2	–	–	–	–	–

N – the number of patients; URT – the upper respiratory tract; LRT – the lower respiratory tract; UT – the urinary tract; S/SCT – skin and/or subcutaneous tissue

A retrospective 12-month analysis of infections was conducted in the studied group of PSS patients receiving long-term pulse CTX treatment. The analysis used data collected during interviews, physical examinations, and additional tests, together with all available medical records. For the needs of the study, the infections were divided into three categories: type, treatment options, localization, and also criteria for their classification according to their severity were established (**Table 2**). In this study the arithmetic mean of infections in each patient was calculated.

Results

In the studied group of patients with PSS treated with CTX pulse therapy, 46 various infections were found in total during the year analysed retrospectively. The following infection types were found: 28 (60.9%) mild infections, 17 (37.0%) moderate infections, and a severe infection in one (2.2%) patient. Only 4 (23.5%) had more than 2 infections a year. In each patient, the mean number of infections in the analysed year was 2.7 ± 3.5 (median: 2). The majority (32 – 69.6%) of infections concerned the respira-

tory system, while the remaining 14 (30.4%) affected the urinary tract. No skin and/or subcutaneous tissue infections were found in the analysed group of patients. Only in one case the infection required hospitalisation and parenteral antibiotic therapy. In three (17.7%) patients no infection was diagnosed in the period covered by observations.

Discussion

In the conducted retrospective analysis of the group of PSS patients treated with intravenously administered CTX, the majority of infections were mild and transient. The patients covered by the assessment presented mainly the respiratory system infections, of which over 80% involved the upper respiratory tract. They were mild and required only a symptomatic treatment. In a population of healthy adults, 2–5 cases of viral acute rhino-sinusitis, including common cold, were noted per year, and this is comparable to the rate of majority of infections in the studied group [17]. Our analysis showed that patients receiving CTX as a long pulse therapy of single 400–800 mg doses every 1–3 month do not develop a significant infection frequently, and severity of most of them possibly does not outbalance scientifically proven advantages of this treatment. Basing on the studied group CTX is not a significant factor increasing a risk of severe infections requiring parenteral treatment and/or hospital admission.

CTX therapy inhibits the immune system; therefore, by definition it should increase frequency and severity of infections. Considering the conducted study, it can be established that it is not so, particularly in a case of standard immunosuppressive PSS treatment. In the analysed group of patients, more than half of infections were mild, not requiring causal treatment, and nearly 20% of patients did not have any infection in the analysed period of time. Only one person suffered a severe infection in form of bronchitis, but it was without complications and resolved with intravenous empiric antibiotic therapy. The conducted analysis was certainly limited by a lack of a relevant control group of PSS patients not receiving immunosuppressive treatment, as well as by inability to obtain details on infection aetiology. Also, it is difficult to compare the results of this study with other reports, as publications on infections in PSS patients chronically treated with CTX are lacking. Nevertheless, the analysis showed that pulse CTX therapy does not increase frequency of severe infections in PSS patients.

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Conflict of interest statement
The authors declare that there is no conflict of interest in the authorship or publication of contribution.

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