ORIGINAL INVESTIGATIONS

Safety and efficacy of 23-valent polysaccharide pneumococcal vaccine in patients with systemic lupus erythematosus

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Objective: *to study the safety and efficacy of the 23-valent polysaccharide pneumococcal vaccine (PPV-23) in patients with systemic lupus erythematosus (SLE).*

Patients and methods. *The study included 75 patients with definite diagnosis of SLE at the age of 19–68 years, 10 (13%) of them had high SLE activity, 18 (24%) – moderate, 42 (56%) – low, in 5 (7%) patients the disease was in remission. PPV-23 was injected subcutaneously in a single dose of 0.5 ml. In 60 patients the follow-up period was ⩾12 months, in 15 – from 2 to 6 months. Patients were examined before and 1, 3 and 12 months after immunization.*

Results and discussion. *In 38 (50.7%) patients, standard local vaccination reactions of mild and moderate severity were noted, in 1 (1.3%) – a general reaction of mild severity, in 2 (2.7%) – mild diarrhea during 1 day, in 1 (1.3%) – a hyperergic reaction of the Artyus phenomenon type, the symptoms were relieved within 7 days. During 12 months of follow-up, neither exacerbations of SLE, reliably associated with vaccination, nor new autoimmune phenomena, were detected.*

After 1 year of observation, the number of responders to vaccination was 58%, non-responders – 42%. The duration and activity of the disease, age over 50 years, glucocorticoid therapy > 10 mg per day, did not significantly affect the vaccine response. There was a decrease in the immune response in patients on biologic DMARDs (bDMARDs) therapy compared to patients without such treatment (43 and 68% of cases, respectively), p=0.058. There was no difference between rituximab and belimumab treated subjects. There was a tendency for the prevalence of vaccination responses among patients, who received bDMARDs <1 year before immunization, as well as among patients in whom this therapy was initiated after the administration of PPV-23. There was a positive trend in decrease of pneumonia, acute and exacerbations of chronic bronchitis episodes and sinusitis.

Conclusion. *Sufficient immunogenicity, good tolerability and clinical efficacy of PPV-23 in patients with SLE, including those who received combined immunosuppressive therapy, have been shown. The use of bDMARDs reduces the number of patients with a vaccine response. The number of responders to vaccination increases when immunization is carried out before the initiation of therapy with bDMARDs or when this therapy is initiated <1 year before immunization. Further long-term prospective studies in large patient cohorts are required.*

Key words: *systemic lupus erythematosus; pneumonia; vaccination; 23-valent polysaccharide pneumococcal vaccine; immunosuppressive therapy; biologic DMARDs.*

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According to the WHO, pneumococcal infection (PI) is recognized as the most dangerous of all infectious diseases preventable by vaccine prophylaxis (VP). It is characterized by a high prevalence, as well as an increase in resistance to a number of antimicrobial drugs. Before the introduction of universal vaccination against PI, it caused 1.6 million deaths annually, including from 0.7 to 1 million children [1].

In the Russian Federation, vaccination against PI of all adults over 50 years old, as well as patients of risk groups is included in clinical guidelines and standards of medical care for a number of clinical specialties and is aimed at reducing morbidity, disability and mortality from this infection [1–7].

According to the recommendations of the EULAR (European League Against Rheumatism) experts, immunization with pneumococcal vaccines is the most important factor in prevention of severe respiratory infections in patients with immunoinflammatory rheumatic diseases (IMRD), including systemic lupus erythematosus (SLE), and is strongly recommended for these patients [8, 9].

In SLE patients, an important aspect of vaccination is its safety and efficacy, especially against the background of long-term and active immunosuppressive therapy.

The aim of the study was to assess the safety and efficacy of the 23-valent polysaccharide pneumococcal vaccine (PPV-23) in patients with SLE.

Patients and methods. The study included 75 patients with SLE who met the diagnostic criteria of ACR (American College of Rheumatology) 1997 for SLE and the criteria SLICC (Systemic Lupus International Collaborating Clinics) / ACR 2012 [10], among whom women of 19–68 years old predominated (88%). The duration of SLE ranged from 6 months to 42 years, its activity, assessed by the SLEDAI index (Systemic Lupus Erythematosus Disease Activity Index) in the 2000 modification [11], was high in 10 (13%) patients, medium – in 18 (24%), low –

in 42 (56%) patients, and 5 (7%) patients showed remission. PPV-23 was injected subcutaneously in a single dose of 0.5 ml. The follow-up period in 60 patients reached ⩾12 months, in 15 – from 2 to 6 months.

Out of 60 patients examined during this year, 58 received glucocorticoids (GC) 5–40 mg/day in terms of prednisolone, 46 – hydroxychloroquine (HCh), 33 – cytostatics (CSs), 23 – biologics (bDMARDs), including rituximab (RTM) – 12 patients, belimumab (BLM) – 10 patients, and 1 patient received a combination of RTM and BLM.

Patients were examined at baseline, 1, 3 and 12 months after vaccination. Standard clinical and laboratory studies were carried out, determination of the level of antibodies (ABs) to cell wall polysaccharides of Streptococcus pneumoniae in the blood serum using commercial kits VaccZymeTM PCP Ig 2 (The Binding Site Ltd, Birmingham, UK). For each patient, the vaccine response rate (VRR) was calculated – the ratio of AB levels at the time of the 2nd and 3rd visits to the baseline level. The immune response to the vaccine was regarded as sufficient if a year after vaccination the level of ABs was at least 2 times higher than the initial level.

Statistical analysis was performed using the Statistica software package, version 12.0 (StatSoft Inc., USA). Quantitative data are presented as median and interquartile range (Me [25th; 75th percentile]). For statistical processing of the results, the Mann–Whitney and Wilcoxon tests were used. Differences were considered significant at p⩽0.05.

Results

Safety. An assessment of the tolerance of vaccination, including the development of post-vaccination reactions in the first 2–3 months, showed that 33 (44%) of 75 patients had no vaccination reactions, 38 (50.7%) had local reactions of mild and moderate severity (pain, swelling, flushing of the skin at the injection site) lasting from 2 to 7 days, 1 patient (1.3%) had general weakness for 1 month, and 2 patients (2.7%) – mild diarrhea for 1 day. Vaccinal reactions were typical and completely reversible and did not require additional treatment. One patient (1.3%) developed a hyperergic reaction of the Arthus phenomenon type, the symptoms were relieved after 1 week with the use of antihistamines and topical GCs.

During the follow-up period (12 months), not a single case of exacerbation of SLE directly related to vaccination was detected, that is, in the first 2–3 months after vaccination. The dynamics of the indicators of immunological activity and the SLEDAI-2K index during the year after immunization are presented in Table. 1. Within the follow-up period (12 months) 7 patients developed a moderate exacerbation of the disease, but not in the period immediately following the introduction of the vaccine: 3 patients – 3.5–5 months after the vaccination, 4 patients – 12 months later. In 4 patients, exacerbation of SLE developed with a decrease in the dose of GC, in 1 patient – after psychological stress; in 1 patient – against the background of persistently high immunological activity due to insufficient therapy, and in 1 more patient – without an increase in immunological activity. An increase in the activity in 4 patients was manifested by skin rashes and articular syndrome, in 1 – by panniculitis, in 2 – by leukopenia. All these symptoms were observed earlier, with previous exacerbations of the disease, and were quickly stopped by a moderate increase in GC dose.

In 33 (55%) of 60 patients, vaccination was carried out against the background of low SLE activity, in 12 patients (20%) – moderate activity, in 9 (15%) – high activity, in 6 (10%) – during remission. Table 2 shows the main indications for vaccination in patients with high SLE activity.

Table 1. Dynamics of immunological parameters and SLEDAI-2K index after vaccination (n=0)

Follow-up period	Anti-DNA <20 IU/ml	C3 0.9–1.8 g/L	C4 0.1–0.4 g/L	SLEDAI-2K
1st visit (baseline)	25.8 [4.9; 65.1]	0.86 [0.8; 1.05]	0.14 [0.1; 0.9]	4 [2; 6]
2nd visit (after 1–3 months)	26.1 [7.3; 54.2]	0.96 [0.8; 1.1]	0.17 [0.13; 0.19]	2 [2; 4]
3rd visit (after 12 months)	17.5 [5.0; 51.7]	0.93 [0.8; 1.06]	0.16 [0.12; 0.19]	2 [2; 4]

Note. Data are presented as Me [25th; 75th percentile].

Table 2. Indications for vaccination with high SLE activity (n=9)

Indications for vaccination	Number of patients	SLEDAI-2K
Cyclophosphamide (CP) therapy and		
frequent upper respiratory tract infections	1	14
recurrent bronchitis	1	18
Planned therapy with RTM and		
recurrent bronchitis	1	14
recurrent pneumonia	1	14
Previous therapy with RTM and recurrent pneumonia	1	12
Previous therapy with RTM and BLM and		
frequent upper respiratory tract infections	1	13
RTM therapy and frequent upper respiratory tract infections	3	12; 14; 12

Table 3. Dynamics of the level of pneumococcal antibodies within 12 months after vaccination (n=60)

Indicator	Initially (n=60)	After 1-2 months (n=54)	After 12 months (n=60)
Concentration AB, mg/L, Me [25th; 75th percentile]	63.5* [34.9; 101.2]	323.5** [73.8; 454.7]	140.2*** [75.5; 328.6]
Patients with immune response, %		**78**	**58**

Note. p*-**; p*-*** <0.05.

Pronounced post-vaccination reactions, as well as deterioration of patients' condition with high SLE activity, were not noted. All patients receiving anti-B-cell therapy (n=5) and CP therapy (n=2) had a response to vaccination.

Immunogenicity. One-two months after immunization, 78% of patients showed more than a twofold increase in the concentration of pneumococcal antibodies; after 12 months of observation, antibodies were detected in 35 (58%) patients, and in 25 (42%) no response to vaccination was recorded. The dynamics of the concentration of pneumococcal antibodies is presented in Table. 3.

The severity of the vaccine response did not depend on the age of the patients: among people under 50 years old (n=46), the proportion of those who responded to vaccination was 52.2%, among people over 50 years old (n=14) – 50%.

The duration of SLE also did not affect the immune response: with a disease period of up to 5 years, an adequate vaccine response was observed in 47.6%; from 5 to 10 years – in 66.7%; over 10 years – in 55.6 % of patients.

In patients who were immunized against the background of SLE remission, an adequate vaccine response was found in 50% of cases, against the background of low activity – in 52%, moderate activity – in 50% and high activity – in 100%.

Analysis of the effect of bDMARDs on vaccine response showed that the use of anti-B-cell drugs reduced the number of responders to immunization compared to that in the absence of such treatment: 43% and 68%, respectively (p=0.058). The

Table 4. Duration of bDMARD therapy and vaccine response (n=23)

Indicator	Duration of bDMARD therapy before vaccination ≤12months (n=10)	Duration of bDMARD therapy before vaccination >12 months (n=8)	Initiation of bDMARD therapy after vaccination (n=5)
Patients who responded to vaccination, n (%)	5 (50)*	1 (12.5)**	4 (80)***

Note. p*-** =0.2; p*-***=0.6; p**-***=0.06.

Table 5. Respiratory infections in SLE patients before and after vaccination (n=60)

Indicator	Within 12 months prior to vaccination		Within 12 months after vaccination		p
	abs.	%	abs.	%	
URTI	10	19.2	7	11.7	0.3
LRTI:	28	46.7	8	13.3	0.001
including pneumonia, including recurrent (2-3 episodes)	11 4	18.3 6.7	4 0	6.7 0	0.09
acute bronchitis	11	18.3	3	5	0.07
exacerbation of chronic bronchitis	6	10	1	1.7	0.2

Note. URTI – upper respiratory tract infections.

duration of bDMARD therapy also influenced the vaccine response.

Among patients who received bDMARDs before vaccination for > 12 months, the number of responders to immunization was the lowest (12.5%), while among patients treated for ⩽12 months, it was 50%. Moreover, the severity of the response in the latter did not depend on the duration of bDMARD therapy after vaccination. The maximum number of individuals with an adequate immune response (80%) was recorded among patients who initiated this treatment after 1; 2.5; 4 and 6 (in 2 cases) months after vaccination (Table 4). There were practically no differences with RTM and BLM therapy: 50% and 40% of individuals with an adequate immune response, respectively. Thus, there was a tendency towards a predominance of vaccine responders among patients who received bDMARDs <1 year before vaccination and those who were prescribed this treatment after immunization.

Adding cytostatics (CSs) to GC therapy did not reduce the number of patients who responded to vaccination: 65% and 67% respectively. Similar results were observed when CSs were added to bDMARD and GC therapy: 44% and 43% of respondents, respectively.

There were no differences between patients who received GCs at a dose of > 10 mg / day during the vaccination period (n = 22) and <10 mg / day (n = 36): the immune response was registered in 59% and 58% of cases, respectively.

Data on the clinical efficacy of vaccination in 60 patients with SLE are presented in Table. 5

Within a year after vaccination, a significant decrease in the number of lower respiratory tract infections (LRTI) was noted compared to the same period before vaccination (13.5% and 46.7%, respectively; p = 0.0001); there was a tendency to a decrease in the episodes of pneumonia, not a single case of repeated pneumonia was identified. Within a year after vaccination, 4 (6.7%) patients developed non-severe pneumonia, all of these patients had predisposing factors for the development of LRTI: anti-B-cell therapy with no adequate vaccine response (in 3 patients), interstitial lung disease (in 1 patient), job and presence of preschool children, which increased the risk of viral / bacterial infections (in 3 patients).

In 60 patients, the dynamics of immunological markers of SLE was analyzed within a year after vaccination. During this time, no evidence of a significant increase in the immunological activity of the disease was obtained. After vaccination, not a single new autoimmune phenomenon, both laboratory and clinical, was detected. In the first 3 months after immunization, in isolated cases, there was a transient increase or decrease in the level of immunological markers of SLE (anti-DNA, antinuclear factor, C3- and C4-complement fractions), followed by a return to baseline values without any symptoms of exacerbation of the disease.

Discussion. PPV-23 has been available since the early 1980s. Long-term experience with the use of PPV-23 confirms its safety in relation to serious post-vaccination complications. Minor vaccine reactions, such as temporary redness, swelling and pain at the injection site, occur in 30–50% of patients. An increase in body temperature to subfebrile values, drowsiness are observed infrequently. Very rarely, there may be enlargement of lymph nodes, diarrhea, vomiting, extremely rarely – anaphylactic reactions (like with any other drug) [12].

Vaccination of patients with immunoinflammatory rheumatic diseases (IMRDs) which is primarily aimed at preventing severe LRTIs, is gaining more and more supporters both among doctors and among patients [13–15]. As vaccination against PI is being introduced into rheumatological practice, the evidence base for the safety of such vaccines in IMRD is increasing: in general, they are well tolerated, and neither exacerbate the underlying disease, nor contribute to the development of new autoimmune phenomena. Research conducted, including that at the V.A. Nasonova Research Institute of Rheumatology, indicates high clinical efficacy and safety of PPV-23 in patients with IMRD. The results of our own studies have shown that after vaccinating patients with rheumatoid arthritis (RA) with PPV-23, the frequency of local vaccination reactions was 35% [16–19]. In this study, local reactions were observed in 50.7% of patients, which may reflect the increased activity of the immune system in SLE. The Arthus phenomenon, which developed in 1 patient after the administration of the vaccine, is a rare post-vaccination reaction that was stopped within a few days without serious consequences.

Most researchers note the absence of a significant effect of PPV-23 immunization on SLE activity according to the SLEDAI scale [20–22]. In our study, we did not register a single case of exacerbation of SLE or a new autoimmune phenomenon that was reliably associated with the vaccination.

In the general population, within 2–3 weeks after immunization with PPV-23, at least 80% of the vaccinated individuals have the level of protective antibodies at least 2 times higher than initially. In our study, 41 (68%) patients received combined immunosuppressive therapy, which included not only GC and HCh, but also CS and bDMARD. Nevertheless, a significant increase in the concentration of specific antibodies 1–2 months after the vaccination was noted in 78% of patients, and after one year it was sustained in 58%, which is consistent with the data of other authors who studied the immunogenicity of PPV-23 in RA and SLE [23].

In the present study, GC administration at doses > 10 mg / day did not lead to a decrease in the number of people with a vaccine response compared to the rest of the patients who took these drugs in lower doses (58% and 59%, respectively), which is con-

sistent with the results obtained earlier in RA patients in whom GC therapy did not adversely affect the rates of vaccination response [16].

A full-fledged immune response was recorded less frequently against the background of bDMARD therapy than without these drugs (42% and 58%, respectively; p = 0.058). The results obtained are consistent with the observations of other authors, indicating a negative effect of bDMARDs, in particular anti-B-cell drugs, on the immunogenicity of pneumococcal vaccines [24–26].

When comparing the severity of the negative effect of RTM and BLM on the immunogenicity of the vaccine in our study, no significant differences were found. The effect of the duration of bDMARD therapy on the severity of the vaccine response was analyzed for the first time. There was a tendency to the prevalence of the number of responders to vaccination (80%) among patients in whom bDMARD therapy was started after immunization, as well as among patients who received these drugs <12 months before vaccination (50%). The smallest number of individuals with the immune response was observed among patients who were on bDMARD therapy for > 12 months before the vaccine administration (12.5%).

EULAR experts recommend vaccinating in the inactive phase of the disease so as not to provoke a theoretically possible exacerbation of the disease. However, the need to vaccinate a patient often arises with moderate to high SLE activity, for example, with frequent recurrent LRTIs, including recurrent pneumonia, as well as before the planned intensification of immunosuppressive therapy, in particular, before prescribing bDMARD. Our data indicate the absence of negative dynamics in the condition of patients vaccinated against the background of high and medium SLE activity, both in terms of the SLEDAI index and in terms of the main immunological parameters during 12 months of follow-up. At the same time, their vaccine tolerance was no worse than that of patients with low SLE activity, and the number of responders to immunization did not decrease. In patients with high SLE activity included in our study, 100% vaccine response can probably be explained by the fact that active immunosuppressive therapy, which negatively affects the production of protective antibodies, was only planned or had been started not long before vaccination. These results allow us to discuss the safety of vaccination carried out not only in the inactive stage of the disease, but also against the background of moderate and high SLE activity.

In general, clinical effectiveness of vaccination was confirmed by positive dynamics – a decrease in cases of pneumonia, acute bronchitis and exacerbation of chronic bronchitis, as well as a milder course of pneumonia compared with its previous episodes. In addition, many patients have less frequent acute respiratory viral infections after vaccination.

Conclusion

1. Sufficient immunogenicity and clinical efficacy of PPV-23 in patients with SLE have been shown.

2. Vaccination with PPV-23 is well tolerated and safe for patients with low and moderate SLE activity. If necessary, it is possible to vaccinate patients with high disease activity without increasing the risk of developing adverse events.

3. In the first 3 months after vaccination, in isolated cases, there may be a transient increase or decrease in the level of immunological markers of SLE followed by its return to baseline values. During one year, the dynamics of the main markers of SLE is multidirectional, which reflects instability of immunological parameters in this disease, and not a reaction to the vaccine.

4. RTM and BLM negatively affect the immunogenicity of PPV-23 vaccine, however, if the timing of its administration is correct, the number of patients with a vaccine response increases.

5. Further research is needed to clarify and confirm the results obtained.

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