ORIGINAL INVESTIGATIONS

Portrait of a patient with systemic lupus erythematosus for the prescription of the type I interferon inhibitor anifrolumab

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In recent years the use of monoclonal antibodies that block activity of type I interferon (IFN) or its receptors has become the new approach in the pharmacotherapy of systemic lupus erythematosus (SLE).

Objective: *to characterize patients with SLE treated with the type I IFN receptor inhibitor anifrolumab (AFM, Saphnelo®).*

Material and methods. *The prospective 12-month study included 21 patients with SLE who met the 2012 SLICC criteria. Standard laboratory and immunological markers for SLE were examined in all patients. The SLEDAI-2K index was used to determine the activity of SLE and the CLASI index was used to determine the severity of the mucocutaneous syndrome. Organ damage was assessed using the SLICC/ACR Damage Index (DI). The LupusQol and FACIT-Fatigue questionnaires were used to analyze health-related quality of life (HRQoL).*

Results and discussion. *Female patients prevailed in the study, female/male ratio – 17 (81%)/4 (19%), median age – 31 [27; 46] years, disease duration – 9 [6.0; 11.0] years. The majority of patients (86%) had moderate or high disease activity according to the SLEDAI-2K index. Among the clinical manifestations of SLE, skin and mucous membranes lesions predominated (81%). Non-erosive polyarthritis of varying severity was observed in 66% of cases. Serositis showed 24% of patients (pleurisy, pericarditis), 43% had hematological abnormalities (hemolytic anemia, leukopenia, lymphopenia) and 14% - urinary syndrome (daily proteinuria up to 0.5 g/l and/or urinary sediment – leukocytes/erythrocytes/cylinders up to 5 in the field of view in the absence of urinary tract infection). All patients had immunological disorders. 14% of them were diagnosed with antiphospholipid syndrome (APS) and 43% with Sjögren's syndrome.*

All patients received hydroxychloroquine, 95% received glucocorticoids (GC) from 5 to 60 mg/day, 66% received immunosuppressants (cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate). 33% of patients had anamnesis of treatment with biologic disease modifying antirheumatic drugs (rituximab, belimumab, dual anti-B-cell therapy) and Janus kinase inhibitor baricitinib. All patients experienced a significant deterioration in HRQoL.

Conclusion. *The indications for prescribing AFM to 21 patients with SLE were: active SLE according to SLEDAI-2K and/or CLASI with predominant involvement of skin, its appendages and development of polyarthritis with immunological disorders, intolerance/ineffectiveness of previous standard therapy and inability to achieve low average daily doses of oral GCs. Other clinical manifestations in some patients were: serositis, mild hematological disorders (Coombs-positive anemia, leukopenia), urinary syndrome. AFM could be prescribed for a combination of SLE with secondary APS and Sjögren's syndrome as well as for a high DI SLICC.*

Keywords: *systemic lupus erythematosus; interferon receptors; interferon α; anifrolumab.*

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Systemic lupus erythematosus (SLE) is a systemic autoimmune rheumatic disease of unknown aetiology. It is characterised by the hyperproduction of organ-unspecific autoantibodies against various nuclear components and the development of immunoinflammatory damage to internal organs [1]. The pathogenesis of this complex and heterogeneous disease has undergone considerable revision in recent years. Particular attention has been paid to the dysregulation of interferon (IFN) type I (IFNα and IFNβ) synthesis, leading to its overproduction in patients with SLE [2–4]. The main mechanism of activation of type I IFN synthesis in SLE is impaired clearance of nucleic acids (NA) released from apoptotic and non-tumour cells. This leads to the formation of "interferonogenic" immune complexes, including NA, NA-binding proteins and antinuclear antibodies. This is facilitated by both increased neutrophil extracellular trap (NET) formation, which is characteristic of SLE, and decreased extracellular DNAase activity. [5]. Type I IFN overproduction in SLE is associated with the development of symptoms such as fever, fatigue, pleuritis, haematological disturbances (anemia, neutropenia, lymphopenia, thrombocytopenia), skin and mucosal lesions, myalgia, polyarthralgia, polyarthritis, lupus nephritis, central nervous system changes (headache) [6-10]. According to its molecular characterisation, the hyperproduction of type I IFN in human diseases has been referred to as the "type I IFN gene signature" (IFNGS) [11, 12]. Type I IFNs comprise 17 molecular subtypes, including 13 subtypes of IFNα, as well as IFNβ, IFNκ and IFNω. In the human body, IFN type I acts as a paracrine and autocrine regulator of a variety of biological processes - modulating innate

and acquired immunity, suppressing cell proliferation and viral replication. All IFN type I subtypes bind to a common heterodimeric receptor complex (interferon α/β receptor – IFNAR) consisting of the IFNα receptor (IFNAR1) and the IFNβ receptor (IFNAR2) [3]. In this context, the development of monoclonal antibodies that block the activity of IFN type I or its receptors has become a new approach to the pharmacotherapy of SLE [13–15]. One such drug is anifrolumab (AFM, Safnelo®), a human IgG1κ monoclonal antibody produced in murine myeloma cells (NS0) using recombinant DNA technology, which binds with high affinity and specificity to the cellular receptor for IFNα (IFNAR1) [16, 17].

In the Russian Federation, AFM was registered on February 27, 2023. It is indicated as an adjunctive therapy for the treatment of adult patients with active moderate-to-severe SLE in the presence of autoantibodies and inadequate response to standard therapy [18]. AFM was made available to a number of rheumatology centres in Moscow, St. Petersburg, Orenburg, Novosibirsk, Saratov, Volgograd and Rostov-on-Don as part of the early access programme. A total of 48 patients with SLE have been treated with AFM in our country. Almost half of them (n=21) are followed at the FGBNU "V.A. Nasonova Research Institute of Rheumatology". There is no doubt that the question of indications for the prescription of AFM is of great interest to practicing rheumatologists.

The aim of the study is to characterize patients with SLE who need to be prescribed AFM, which is the type I INF inhibitor.

Materials and methods. AFM was provided by V.A. Nasonova Research Institute of Rheumatology under early access programme. The "Research programme to study the efficacy and safety of AFM in adult patients with moderate-to-severe SLE" was approved by the local ethics committee of the V.A. Nasonova Research Institute on September 8, 2022 (meeting minutes #17). A total of 21 patients with confirmed SLE who met the SLICC (Systemic Lupus International Collaborating Clinics) 2012 criteria were enrolled in the study at V.A. Nasonova RIR. [19]. The patients were followed for 12 months.

Inclusion criteria: a definite diagnosis of SLE; signed informed consent; age over 18 years.

Non-inclusion criteria: active lupus nephritis and involvement of the nervous system (as AFM is not approved for these indications).

All patients were assessed for disease activity using the SLEDAI-2K index (Systemic Lupus Erythematosus Disease Activity Index-2000) [20] and the severity of the cutaneous mucosal syndrome using the CLASI (Cutaneous Lupus Disease Area and Severity Index) [21, 22], irreversible organ damage using the SLICC/ACR (Systemic Lupus International Collaborating Clinics / American College of Rheumatology damage index) [23], health-related quality of life (HRQoL) using the LupusQol and FACIT-F (Functional Assessment of Chronic Illness Therapy - Fatigue Scale) questionnaires, and concomitant treatment. Standard laboratory tests were performed before enrolment and during the follow-up, including complete blood count and urine analysis, determination of immunological markers of SLE: antibodies to DNA (aDNA), antinuclear factor (ANF) on Hep2 cells, complement components C3 and C4, IgM and IgG antibodies to cardiolipin, IgM and IgG antibodies to β2-

Table 1. Characteristics of patients enrolled into the study (n=21)

Characteristic	Parametrs
Age, years, Me [25th; 75th percentile]	31 [27; 46]
Sex:	
female/male, n (%)	17 (81)/4 (19)
Disease duration, years, Me [25th; 75th percentile]	9 [6.0; 11.0]
SLEDAI-2K, M±σ	8.8±4.7
SLE activity by SLEDAI-2K, n (%):	
low	3 (14)
moderate	13 (62)
high	5 (24)
CLASI, M±σ	8.6±8.2
CLASI, n (%):	
no activity	4 (19)
mild	10 (48)
moderate	4 (19)
severe	3 (14)
DI SLICC/ ACR, M±σ	2.2±1.5
DI SLICC/ ACR, n (%):	
No damage	3 (14)
low	3 (14)
moderate	13 (61)
high	2 (10)
SLE treatments, n (%):	
GC (prednisolone)	20 (95)
Antimalarials	21 (100)
Cytotoxics:	**14 (66)**
Cyclophosphamide	5 (24)
Mycophenolate	7 (33)
Azathioprine	5 (21)
Methotrexate	8 (38)
Biologics 6 (32)	
Rituximab	2 (9)
Belimumab	2 (9)
Belimumab after rituximab	2 (9)
Baricitinib	**1 (5)**
SLE treatments during the study:	
GC (prednisolone) M±σ	10.7±5.6
GC, n (%)	21 (100)
GC 10 мг/сут, n (%)	11 (52)
HCH, n (%)	**16 (76)**
Cytotoxics, n (%)	**7 (33)**
Anticoagulants, n (%)	**4 (19)**

Note. GC, glucocorticoids; HCH, hydroxychloroquine; Biologics, genetically engineered biological drugs; JAK, Janus kinase.

Table 2. Clinical and laboratory manifestations of SLE, included in the 2012 SLICC criteria at the time of enrollment

Clinical characteristics	Patients, n (%)
Acute cutaneous lupus erythematosus (ACLE)	10 (48)
Subacute cutaneous lupus erythematosus (SCLE)	2 (9)
Chronic cutaneous lupus erythematosus (CCLE)	1 (5)
ACLE + CCLE	5 (24)
Oral ulcers	7 (33)
Non-scarring alopecia, including: diffuse/focal	10 (48) 6 (29)/4 (19)
Nonerosive arthritis	14 (66)
Serositis	5 (24)
Urinary syndrome	3 (14)
Hemolytic anemia	4 (19)
Leukopenia or lymphopenia	5 (24)
Immunological disorders, including: increase in ANA titers ANA >1/1280 anti-dsDNA+ анти-Ro/SSA+ antiphospholipid antibodies + hypocomplementemia Isolated positive Coombs test	21 (100) 21 (100) 14 (66) 14 (66) 8 (38) 4 (19) 9 (43) 3 (14)
Antiphospholipid syndrome	3 (14)
Sjögren's syndrome	9 (43)
Parenchymal parotitis	6 (29)
Dry keratoconjunctivitis	5 (24)

Note. Anti-dsDNA are antibodies to double-stranded DNA.

glycoprotein 1.

The activity of SLE by SLEDAI was scored as follows: 0 - no activity, 1 to 5 – low, 6 to 10 – moderate, 11 to 19 – high, and >20 – very high activity [20]. CLASI of 0 to 9 was considered mild, 10 to 20 moderate and 21 to 70 severe skin lesions [22]. SLICC/ACR damage index had the following gradations: 0 – no lesions, 1 – mild, 2 to 4 – moderate, and >4 severe damage. The LupusQol and FACIT-F questionnaires, completed by the patients independently, were used to assess quality of life. The LupusQol questionnaire contains 34 questions grouped into 8 scales: physical health, emotional health, body image (perception of one's own body and how the patient believes others perceive it), pain, planning, fatigue, intimate relationships, and dependence on others. [24]. The worst quality of life on the LupusQoL questionnaire corresponds to 0 and the best corresponds to 100. The intimate relationships and fatigue scales of this questionnaire were not scored – the former because of the prevalence of 'not applicable' responses and the latter because of the use of the FACIT-F fatigue scale, which according to our experience is more sensitive for this indicator.

The FACIT-F consists of 13 questions, each rated on a Likert scale from 0 (not fatigued) to 4 (very fatigued) [25]. All responses to the questions are summed, with responses to questions An5 and An7 summed in reverse order. The final total score is divided by 13. The maximum possible score of 52 indicates no fatigue and good HRQoL. There are four degrees of fatigue: no fatigue (40-52 points), mild fatigue (27-39 points), severe fatigue (14–26 points) and very severe fatigue (0–13 points) [26].

Antiphospholipid syndrome (APS) was diagnosed according to the international classification criteria [27], Sjцgren's syndrome – according to the Russian recommendations of 2001. [28]. Signs confirming the diagnosis of Sjцgren's syndrome were complaints of dry mouth and/or eyes, and/or a history of recurrent parotitis, and/or the detection of ANP, rheumatoid factor, and/or antibodies to the cytoplasmic antigen Rho/SSA (anti-Ro/SSA).

Statistical analysis. In the case of normal distribution, mean (M) and standard deviation (σ) were determined. In the case of non-normal distribution, median and interquartile range (Me [25th; 75th percentiles]) were determined. Differences were considered statistically significant at $p<0.05$.

Results. Table 1 shows the characteristics of the SLE patients treated with AFM. Females predominated, the female/male ratio was 17(81%)/4 (19%), median age was 31 [27; 46] years, and disease duration was 9 [6.0; 11.0] years.

The majority of patients (86%) had moderate or high SLEDAI-2K activity (see Table 1). Skin and mucosal changes were the most common clinical manifestations of SLE (81%). Severe or moderate skin lesions according to the CLASI index were observed in 33% of cases. Signs of acute cutaneous lupus erythematosus (ACLE), such as butterfly erythema, multiple erythematous rashes, maculopapular rash, were seen in 48% of patients, and a combination of ACLE and chronic cutaneous lupus erythematosus (CCLE) was seen in 24%, (including panniculitis, capillaritis, discoid lupus erythematosus), 9% had manifestations of subacute cutaneous lupus erythematosus (SCLE), and 5% had CCLE in the form of discoid rash (Table 2). Almost half of the patients had non-scarring alopecia (diffuse or focal) at the start of treatment, and 33% had ulcerative stomatitis. Nonerosive polyarthritis of varying severity was present in 66% of cases, and was the main indication for inclusion in the study in 4 patients (19%). In addition, serositis (pleurisy, pericarditis) was found in 24% of patients, haematological disorders (haemolytic anaemia, leucopenia, lymphopenia) in 43%, urinary syndrome (daily proteinuria up to 0.5 g/L and/or urine sediment - leucocytes/erythrocytes/cylindruria up to 5 in the field of view in the absence of urinary infection) in 14%. All patients had marked immunological disturbances. High ANP titres were found in 66%, increased aDNA levels in 66%, anti-Ro/SSA in 38%, antiphospholipid antibodies (aPL) in 19%, hypocomplementemia on C3 and C4 in 43%, positive Coombs reaction in the absence of haemolytic anaemia in 14%. APS was diagnosed in 14% of patients, Sjцgren's syndrome in 43% (parenchymatous parotitis in 29%, dry keratoconjunctivitis in 24%).

Irreversible organ damage was detected in 86% of patients (see Table 1). The SLICC/ACR damage index ranged from 2 to 4 points (mean – 2.2±1.5 points). The structure of irreversible organ damage was dominated by changes related to GC therapy: cataract, aspetic necrosis, osteoporosis, diabetes mellitus (Fig. 1).

During the course of the disease, all patients received HCH and 95% received GC at various doses (5 to 60 mg/day; see Table 1). Immunosuppressive drugs (cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate) were used in 66% of the cases and were discontinued due to lack of efficacy or poor tolerability. Biologics (rituximab, belimumab, dual anti-

B-cell therapy) and the JAK inhibitor baricitinib were used in 33% of patients with a history of secondary ineffectiveness or adverse events. At the start of AFM therapy, all patients were receiving GC at a mean dose of 10.7±5.6 mg/day, with 52% of patients receiving >10 mg/day. One patient with lupus panniculitis was prescribed GC for the first time. Only 76% of patients were able to take HCH, 24% discontinued because of retinal angiopathy or development of an allergic reaction. Treatment with immunosuppressants was continued in 33% of patients, and indirect anticoagulants due to APS or a history of thrombosis in – 19%.

Health related Quality of life (HRQol) was significantly impaired in all patients. A significant decrease was observed in 6 scales of the LupusQoL questionnaire (Fig. 2), with the most pronounced decrease in the scales "planning" and "body image" (to 39.2±17.2 and 58.5±24.2, respectively).

Low quality of life was also confirmed by the FACIT-F questionnaire. Tiredness/fatigue was absent in only 1 patient. Very severe (38%) and severe (33%) fatigue was most common (Fig. 3).

The presented data demonstrate that the indications for the addition of AFM at a dose of 300 mg intravenous drip monthly to the standard therapy in 21 patients with SLE observed at the V.A. Nasonova Research Institute of Reumatology, were as follows: 1) SLEDAI-2K activity index values >5 points (86%) and/or high CLASI index values. The clinical picture of SLE was dominated by lesions of the skin and its appendages (81%) and polyarthritis (66%), with marked immunological disturbances. Some patients also had serositis, non-serious haematological disorders (Coombs-positive anaemia, leucopenia), urinary syndrome (daily proteinuria up to 0.5 g/L and/or urinary sediment leucocytes/erythrocytes/cylinderuria up to 5 in the field of view in the absence of urinary infection). The combination of SLE with secondary APS and Sjögren's syndrome was not a contraindication to the use of AFM;

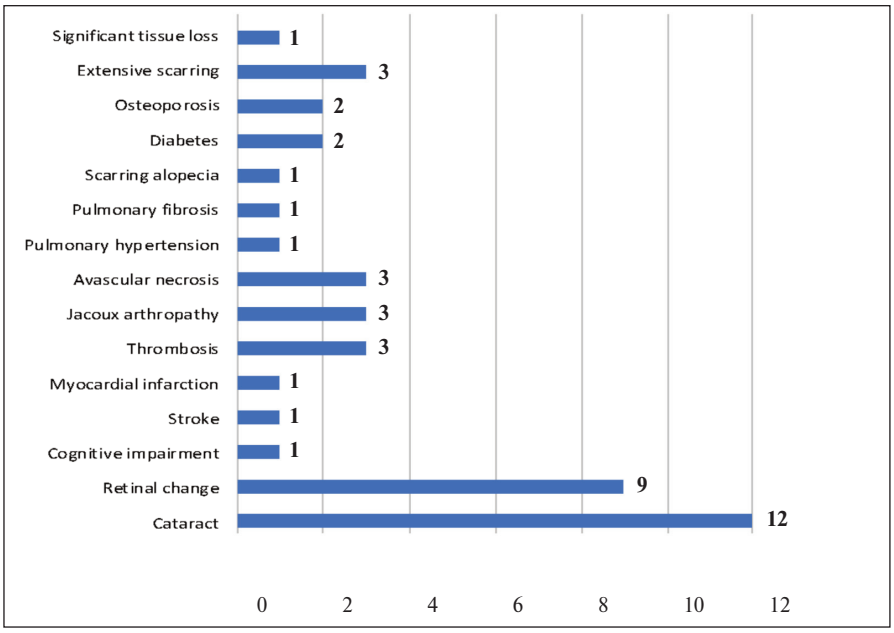

Fig. 1. *Irreversible organ damage in 18 patients with SLE (parameters included in the SLICC damage index)*

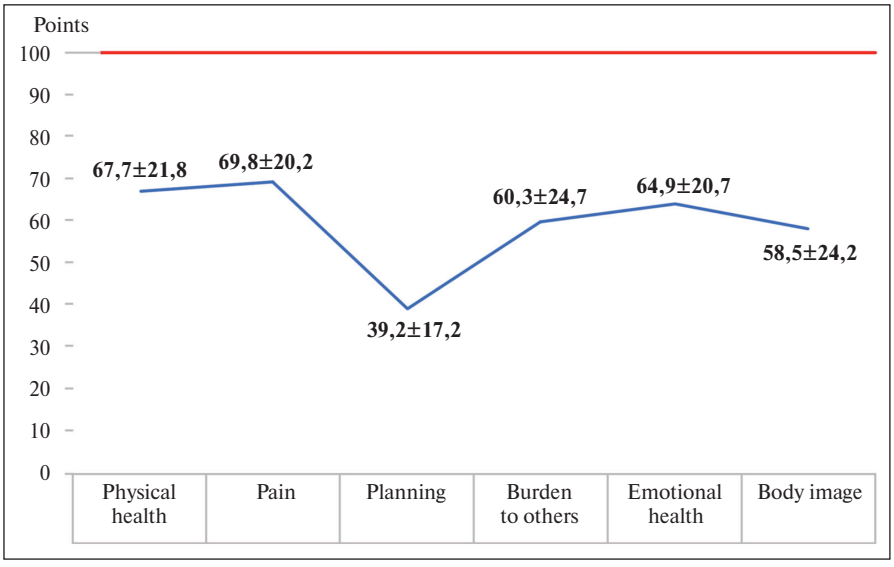

Fig. 2. *HRQoL in 21 patients with SLE before AFM prescription according to the LupusQol questionnaire, M±σ*

2) High SLICC/ACR damage index (DI) with moderate to high SLEDAI-2K activity;

3) intolerance/inefficacy of previous standard therapy with preserved RAS activity;

4) High dose of GC required to maintain low SLE activity;

5) Low quality of life, signs of fatigue/tiredness in the context of SLE activity and high maintenance doses of oral GC.

Discussion. To date, four randomised clinical trials (RCTs) have been conducted worldwide to investigate the efficacy and safety of AMF in patients with SLE: MUSE (phase II), TULIP-1, TULIP-2 and TULIP-LTE (phase III), which resulted in the drug being approved for use in patients with moderately to severely active SLE. The clinical trial phase has been completed and it is now necessary to determine the place of AMF in the treatment of patients with SLE in real-world clinical practice. The first long-term placebo-controlled study in SLE, conducted during the COVID-19 pandemic, has also been completed [29]. Given the chronic nature of SLE and the need for long-term treatment, determining the long-term safety and efficacy of treatment is of great importance. Results from the 52-week phase III TULIP-1 and TULIP-2 studies, the subsequent 3-year long-term extended follow-up, and the 3-year open-label extension of phase II MUSE study confirmed an acceptable long-term safety profile of AFM in SLE, in addition to a sustained reduction in disease activity

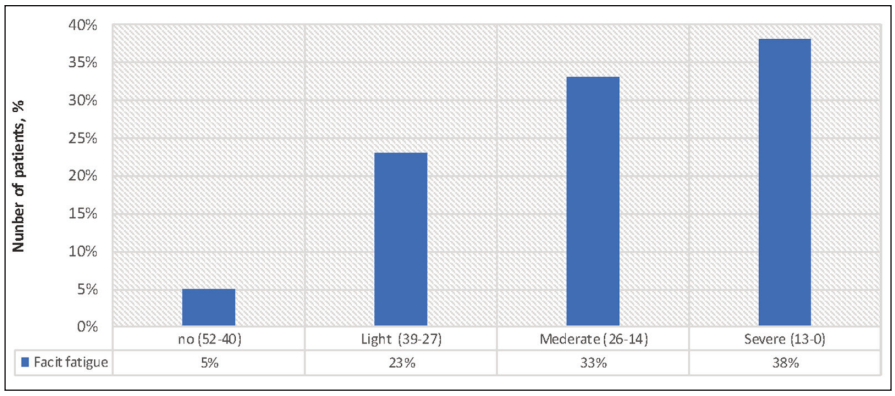

Fig. 3. *Severity of fatigue in 21 patients with SLE before administration of AFM according to the FACIT Fatigue (FACIT-F) Scale*

and reduced GC use. Overall, the data showed a favourable risk-benefit profile for long-term use of AFM in patients with moderately to highly active SLE [29].

The aim of our study was to characterise patients with SLE treated with the interferon type I receptor inhibitor AFM. Patients were recruited according to inclusion criteria based on RCT data. Patients who were positive for ANF, aDNA and/or antibodies to Sm antigen were selected for the MUSE study (phase II). The mandatory criterion was at least moderate SLE activity (SLEDAI-2K ≥6) and the clinical component of the index had to be SLEDAI-2K≥4. Patients with active lupus nephritis and severe neuropsychiatric manifestations of SLE were excluded [30]. Immunological abnormalities and ANP positivity were also mandatory inclusion criteria in the present study. All our patients were positive for ANF, most of them had high levels of aDNA and/or antibodies against Sm antigen, anti-Ro/SSA. Moderate SLE activity (SLEDAI-2K ≥6) was observed in 86% of patients (see Table 1), with a clinical component corresponding to SLEDAI-2K≥4. Patients with low SLEDAI-2K tended to have moderate to severe CLASI skin lesions. The LupusQol was used to assess quality of life, as it is the only specific questionnaire for patients with SLE validated in the Russian Federation [31] and was also used in the MUSE study (phase II). Inclusion criteria in TULIP-1 [32] and TULIP-2 [33] were similar to those in MUSE (phase II), but stable standard therapy with GC, HCH and immunosuppressants was a prerequisite for inclusion. All patients in our study also received combination therapy with GC and HCH or GC and immunosuppressants or GC, HCH and immunosuppressants. The frequency of GC/HCH/immunosuppressant prescription was 100%/76%/33% in our patients and 78%/66%/48% in the TULIP-2 group, respectively. The number of patients receiving oral GC at a dose >10 mg/day in this study was comparable to that in TULIP-2 (52% and 48%, respectively). It should be noted that our patients had a high SLICC DI ranging from 2 to 4 points (mean 2.2±1.5 points), whereas this index averaged only 0.5±0.9 points in the TULIP-2 group. A high DI in our observation was associated with more frequent use of GC and longer disease duration than in the TULIP-2 group. When prescribing AFM, we selected those disease phenotypes for which an IFN type I inhibitor has been shown to be effective in international clinical trials. When enrolling patients, particular attention was paid to SLE-associated skin and mucosal lesions. In these patients, all clinical trials showed a significant effect from week 12 of treatment. The CLASI index, which was initially ≥10 points, decreased by almost 50% by week 12 [33]. This explains our selection of patients with active cutaneous manifestations of SLE (the majority of the group – 86%). AFM had no less significant effect on joint lesions in SLE. According to TULIP-1, TULIP-2 and MUSE (phase II) data, the number of swollen and painful joints decreased by 50% by week 52 of treatment [31–33]. In our group, 19% of patients had predominant joint involvement. In the TULIP-LTE study, GCs were discontinued in 36.4% of patients by the fourth year of AFM therapy [29]. As shown in Table 1, all our patients were receiving GC and in 52% of them the GC dose was >10 mg/day; the aim of AFM therapy was to reduce the GC dose in the context of decreasing SLE activity. According to the TULIP-LTE data, there was an improvement in quality of life and fatigue during the study, which gives hope for an improvement in these parameters in our patients as well.

Finally, the question arises: is there any difference between the profiles of patients who need to be prescribed belimumab and AFM? Only real-world clinical practice can answer this question. Two interesting papers have recently been published comparing the data from international clinical trials on the efficacy and safety of belimumab (BLISS-52 and BLISS-76) and AFM (TULIP-1, TULIP-2 and MUSE, phase II) [34]. I.N. Bruce et al [34] conclude that in patients with moderate to severe SLE, AFM administration is more likely to achieve a reduction in disease activity than belimumab. At the same time, B. Neupane et al [35] believe that the response to treatment with belimumab and AFM in SLE patients is similar up to week 52, and that it is still not possible to identify a clinically significant advantage of either drug. In our opinion, such a clinically significant advantage of AFM may be not only its efficacy in improving joint manifestations, but also its rapid effect on the skin manifestations of SLE.

Conclusion. Thus, in the present study, the indications for AFM administration were SLEDAI-2K and/or CLASI active SLE with predominant involvement of the skin and its appendages and development of polyarthritis with immunological dysfunction, intolerance/inefficacy of previous standard therapy and inability to achieve low average daily doses of oral GCs. Additional clinical manifestations in some patients were: serositis, non-serious hematological disorders (Coombs-positive anemia, leukopenia), urinary syndrome. The administration of AMF was allowed in the case of combination of SLE with secondary APS and Sjцgren's syndrome, as well as in the case of high DI SLICC/ACR.

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