CLINICAL OBSERVATIONS

Rapid achievement of low disease activity during the use of a type I interferon inhibitor in a patient with torpid systemic lupus erythematosus (case report)

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This article describes the experience of using the type I interferon inhibitor anifrolumab (AFM) in a patient with a torpid course of systemic lupus erythematosus. The reason for prescribing AFM was the need for a quick achievement of low disease activity due to a planned hip replacement. Dynamic observational data over a six-month period confirmed that AFM enables a rapid achievement of low disease activity without increasing the dose of glucocorticoids, significantly improve the patient's quality of life and even prepare them for major surgery without exacerbating the underlying process.

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 etiology characterized by hyperproduction of non-organ-specific autoantibodies against various components of the cell nucleus and cytoplasm and the development of immunoinflammatory damage to internal organs. [1] Among the diverse pathogenic mechanisms of SLE, which include activation of both innate and adaptive immunity, impairment of type I interferon (IFN) production plays a crucial role. [2,3] The results of fundamental and clinical studies served as the basis for developing a new approach to drug therapy for SLE, associated with the use of monoclonal antibodies that block the activity of type I IFN or its receptors. [4,5]

One such drug is anifrolumab (AFM), which is a fully human monoclonal antibody IgG1κ that binds to the cellular receptor for IFNα — IFNAR1 (Interferon Alpha And Beta Receptor Subunit 1) with high affinity and specificity. [6,7] The mechanism of action of AFM includes the suppression of IFN-responsive gene expression and proinflammatory cytokines; inhibition of monocyte maturation into myeloid dendritic cells, differentiation of plasmacytoid dendritic cells and B cells, and normalization of the concentration of B-cell cytokines (B cell activating factor belonging to the TNF family, BAFF). [4,5]

In the Russian Federation, the drug was authorized on 27 February 2023 as an add-on therapy for the treatment of adult patients with active moderate to severe SLE with autoantibodies and insufficient response to standard therapy. AFM was made available to a lot of Russian rheumatology centers in Moscow, Saint Petersburg, Orenburg, Novosibirsk, Saratov, Volgograd, and Rostov-on-Don through an early access program. As part of this program, a total of 48 patients with SLE have received treatment, and almost half of them (n = 21) are followed up at V. A. Nasonova Research Institute of Rheumatology.

AFM was also supplied to V. A. Nasonova Research Institute of Rheumatology through the early access program. The "Research Program to Study the Efficacy and Safety of AFM in Adult Patients with Moderate to Severe SLE" was approved by the local ethics committee of V.A. Nasonova Research Institute of Rheumatology on 8 September 2022 (meeting minutes No. 17 dated 8 September 2022).

The inclusion criteria for the study were signed informed consent and age over 18 years, while the non-inclusion criteria were active lupus nephritis and nervous system involvement (since AFM is not approved for use for these indications).

In all patients, the disease activity was assessed using the SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index-2000), [8] the severity of skin and mucosal manifestations was assessed using the CLASI (Cutaneous Lupus Disease Area and Severity Index), [9,10] and irreversible organ damage was assessed using the SLICC/ACR (Systemic Lupus International Collaborating Clinics / American College of Rheumatology damage index), [11] health-related quality of life (HRQoL), and concomitant therapy were also evaluated. Prior to the inclusion in the study and during the observation, the patients underwent laboratory tests, including a complete blood count and urinalysis, tests for immunological markers of SLE: anti-double stranded DNA (anti-dsDNA) antibodies, antinuclear factor (ANF) on Hep2 cells, C3 and C4 complement components, IgM and IgG anticardiolipin antibodies, IgM and IgG anti-β2-glycoprotein I antibodies.

A SLEDAI-2K score of 0 represented no SLE activity, 1 to 5 — low activity, 6 to 10 — moderate activity, 11 to 19 — high ac-

tivity, and >20 — very high activity. [8] A CLASI of 0 to 9 was viewed as mild, 10 to 20 — moderate, and 21 to 70 — severe skin damage. [10] There were the following damage index grades: 0 — no damage, 1 — low, 2 to 4 — moderate, >4 — high. The LupusQoL (Lupus Quality of Life) questionnaire was provided to the patients for self-completion in order to evaluate HRQoL. It contains 34 questions organized into eight domains: physical health; emotional health; body image (perception of one's own body and how the patient believes others view it); pain; planning; fatigue, intimate relationships; and burden to others. [12] The worst and the best HRQoL assessed using the LupusQoL is 0 and 100 respectively.

We present a case of a torpid course of systemic lupus erythematosus (SLE) with recurrent cutaneous and articular manifestations, high immunological activity, the development of adverse events (AEs) while on therapy with corticosteroids (CSs) and the inability to increase their dose to control disease activity (large cumulative dose during the disease course, femoral head avascular necrosis requiring hip replacement surgery). The patient was followed up for a long time at Yaroslavl Regional Clinical Hospital and was referred to V. A. Nasonova Research Institute of Rheumatology for the initiation of AFM therapy.

The patient signed an informed consent to participate in the early access program for receiving AFM therapy, and to publish his photos and medical history data.

Case report

A male patient born in 1998 who completed his schooling; he is single and works as a furniture assembler. The disease onset occurred from February 2015 (while he was living in Pavlodar, Kazakhstan), when the patient started to notice butterfly-shaped erythema on his face, erythematous skin rash in the low neck area, pain in the small joints of the hands, and a body temperature increase to 39 °C for no apparent reason. Diagnostic evaluation (complete blood count) conducted at a local clinic revealed leukopenia (2.6×10^9/L) and increased ESR (50.0 mm/h); the presence of anti-dsDNA >25 IU/mL was detected for the first time (reference range: <25 IU/mL). He was diagnosed with SLE. He was prescribed methylprednisolone (MP) 48 mg/day, hydroxychloroquine 400 mg/day. Intravenous (IV) endoxan 1000 mg and 6-MP 1000 mg administration was conducted on a monthly basis over a period of 7 months. Low disease activity was achieved. In 2015–2016, upon the physicians' recommendations, the dose of MP was reduced to 8 mg/day.

In 2017, the family moved permanently to Uglich town of Yaroslavl region. In January 2018, the patient developed a pronounced SLE exacerbation manifested in fever, generalized erythematous rash on the skin of the face and the trunk, and polyarthritis. Diagnostic evaluation performed at Uglich Central Regional Hospital showed signs of anemia (Hb — 99.0 g/L), leukopenia (2.29×10^9/L), thrombocytopenia (2.29×10^9/L), increased ESR (40.0 mm/h). Urinalysis for the first time demonstrated such abnormalities as WBC in urine (9 per field of view [FOV]), RBC in urine (up to 5 per FOV), and casts (hyaline casts — 3 per FOV).

IV infusions of prednisolone 90 mg daily for 5 days were carried out; the dose of MP was increased to 8 mg/day, and the patient was prescribed omeprazole, rheopolyglukin, and vitamin B6.

From 6 March to 30 March 2018 the patient received therapy at Department of Rheumatology of Yaroslavl Regional Clinical Hospital. The examination confirmed the presence of urinary syndrome — proteinuria (0.45 g/L), hematuria (40-50-60 RBC per FOV), 24-hour urine protein — 2.428 g/day. Nechiporenko urine test (14 March 2024): pH = acidic; WBC — 28,500/mL, RBC — 38,500/mL. Urea — 10.82 mmol/L, creatinine — 120.0 μmol/L. The dose of CS was increased to 50 mg/day as calculated for prednisolone.

In April 2018, the patient was admitted to Department of Nephrology of Yaroslavl Regional Clinical Hospital, where he underwent a kidney biopsy. The conclusion of the histological examination was as follows: Lupus nephritis, class IV-G(A/C), diffuse proliferative endo- and extracapillary nephritis (severe mesangial and endocapillary hypercellularity); diffuse segmental endocapillary karyorrhexis and glomerular fibrinoid necrosis; segmental and circumferential crescents (60%), cellular and fibrocellular (in a 5:1 ratio); complete (3%) and segmental (10%) glomerulosclerosis; mild tubulointerstitial inflammation, multifocal acute tubular epithelial injury without tubulointerstitial fibrosis and arteriolosclerosis. High activity (24 of 24 points), insignificant degree of chronic disease (2 of 12 points). Lupus vasculopathy with immunocomplex deposition, uncomplicated, with involvement of arterioles and small- and medium-sized arteries.

On 20 April 2018, induction therapy for lupus nephritis was started according to the classical regimen: monthly (for 6 months) intravenous administration of 1000 mg of cyclophosphamide (CP). From April through September 2018, the patient received a cumulative CP dose of 6 g, and was switched to IV administration every 3 months. In December 2018, nephrotic syndrome was improved, while minimal urinary syndrome persisted, which was reversed by March 2019 as a result of CP therapy (with normal renal function). By June 2019, a cumulative CP dose of 9 g was administered, and nephritis remission was achieved. The patient was followed up by a nephrologist and a rheumatologist at a local outpatient clinic and was receiving MP 8 mg/day and hydroxychloroquine 400 mg/day.

However, there were annual SLE exacerbations with the development of skin and joint lesions and high immunological disease activity: in 2020, the level of anti-dsDNA was 154.6 IU/mL (reference range: 0–25 IU/mL). Echocardiography performed at the time of the exacerbation showed the signs of pericarditis. Maintenance dose of CS was 8 to 48 mg/day; hydroxychloroquine — 200 to 400 mg/day; during exacerbations the patient received pulse therapy with 6-MP and endoxan 1000 mg, and three sessions of therapeutic plasma exchange were conducted. In 2021, the patient had leukopenia (2.9×10^9/L) and high anti-dsDNA level (121 IU/mL, reference range: 0–25 IU/mL).

Since 2022, the patient has been experiencing pain and restricted hip mobility, and a 'duck-like' gait. Diagnostic evaluation demonstrated bilateral femoral head avascular necrosis, and surgical treatment was recommended. In total, the patient received 21 courses of pulse therapy with 6-MP and CP.

Another exacerbation was registered in the spring of 2023: maculopapular rash on the face (butterfly rash), the neck, upper chest and upper limbs; patchy alopecia, bright palmar capillaritis, polyarthritis of small joints of the hands, high immunological activity: anti-dsDNA — >100 IU/mL (reference range: 0–25 IU/mL), ANF titer, indirect immunofluorescence test — 1/10,240 (reference range: <1/80). He continued receiving MP 4 mg/day and hydroxychloroquine 200 mg/day. He noted a pronounced increase in pain severity and restricted mobility in both hip joints. Taking into account a torpid disease course (recurrent skin lesions, persistently high laboratory and immunological activity), the development of AEs while on therapy with CSs (bilateral femoral

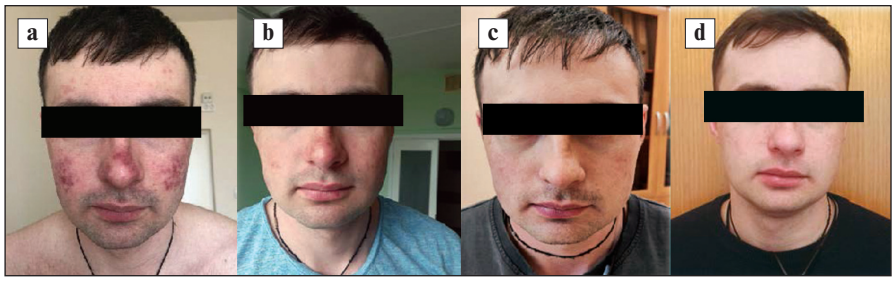


Fig. 1. *Dynamics of skin manifestations of SLE during AFM therapy: a — before the start of therapy; b — after 1 week; c — after 3 months; d — after 9 months*

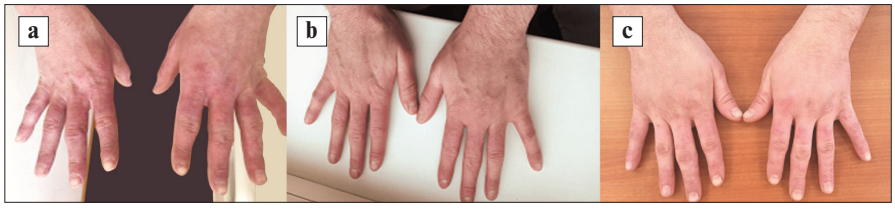


Fig. 2. *Dynamics of capillaritis and polyarthritis during AFM therapy: a — before the start of therapy; b — after 3 months; c — after 9 months*

head avascular necrosis), severe pain and restricted hip mobility, which significantly worsened the quality of life, as well as the inability to achieve low disease activity when increasing the CS dose, and the need for hip replacement surgery, the patient was referred to V.A. Nasonova Research Institute of Rheumatology for hospitalization to initiate AFM therapy.

Admission diagnosis: SLE, subacute course, high activity (SLEDAI-2K = 13), with involvement of the skin (acute cutaneous lupus erythematosus, facial butterfly-shaped skin rash, maculopapular erythematous rash, CLASI A index = 23, CLASI D = 1), vessels (periungual capillaritis, Raynaud's syndrome), joints (polyarthritis of small joints of the hands), hematological (leukopenia, lymphopenia), immunological (anti-dsDNA, lupus anticoagulant, hypocomplementemia by C3 and C4, high level of ANF) disorders. The patient had a history of serositis (pericarditis), splenomegaly, lupus nephritis (grade IV according to kidney biopsy findings in April 2018). SLICC/ACR damage index = 2 (bilateral femoral head avascular necrosis). Complications: bilateral femoral head avascular necrosis, functional class 3.

Dermatologist exam conclusion: facial butterfly-shaped skin rash, maculopapular erythematous rash, palmar capillaritis. Raynaud's syndrome. Small joint polyarthritis, restricted hip mobility; the patient has a pronounced limp. Test results: WBC 2.3×10^9/L, lymphocytes 0.64×10^9/L, proteinuria 0.015 g/L; no sediment, glomerular filtration rate 125 mL/min, ANF 1/5,120, anti-dsDNA 800 IU/mL (reference range: 0–100 IU/mL), C3 0.7 g/L (reference range: 0.9–1.8 g/L), C4 0.09 g/L (reference range: 0.1–0.4 g/L), direct Coombs test 1+, no other immunological abnormalities were detected. SLEDAI-2K activity index — 13 points (rashes — 2, alopecia — 2, arthritis — 4, low complement — 2, elevated anti-dsDNA — 2, leukopenia — 1), CLASI lupus erythematosus activity and severity index A = 23, SLICC damage index — 2 (bilateral femoral head avascular necrosis). Mycophenolate mofetil (MMF) 1000 mg/day was added to the treatment regimen (MP 4 mg and hydroxychloroquine 200 mg).

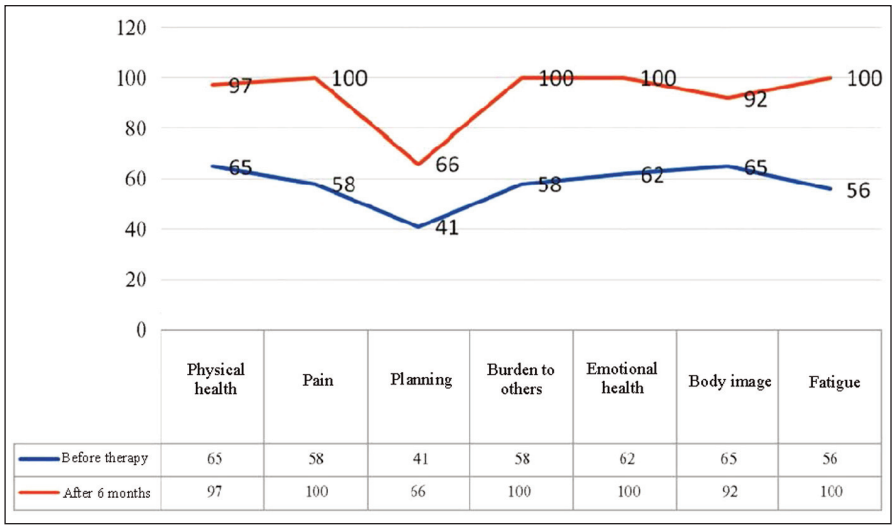
Therapy with AFM was initiated according to the recommended regimen (300 mg IV drip on a monthly basis). No AEs were reported during the first and subsequent infusions of AFM. As early as within the first week of treatment, there was a significant improvement in skin rash, and the lesions continued to improve over a period of one month. According to the patient, within the first three days, his skin acquired a healthy color; he developed a feeling of lightness in his body, and his joint pain gradually began to subside; after the second drug dosing (one month later), the result was stable. Three months after the start of therapy, the SLE skin manifestations were no longer observed (see Fig. 1). The improvement was maintained 6 and 9 months after the start of treatment (see Fig. 1, Fig. 2). By the third month of therapy, the SLEDAI-2K score decreased from 13 to 7 points (persistent alopecia, hypocomplementemia, anti-dsDNA), and by the sixth month, the score decreased to 4 points (immunological disorders — hypocomplementemia and anti-dsDNA) with complete reversal of SLE-related clinical manifestations. Three and six months after the start of AFM therapy, the WBC count (from 2.3×10^9/L to 4.5×10^9/L and 4.8×10^9/L respectively) and lymphocyte count (from 0.64×10^9/L to 0.83×10^9/L and 1.18×10^9/L respectively) were within the normal ranges. At the same time, there was improvement in terms of immunology parameters: a decrease in ANF titer from 1:5,120 to 1:2,560. There was a decrease in the anti-dsDNA levels from 800 IU/mL to 300 and to 468 IU/mL respectively.

The assessment of HRQoL using the LupusQoL six months after the start of therapy demonstrated normalization of domains "Pain", "Burden to others", "Emotional health", "Fatigue", and improvement of domains "Physical health", "Planning" and "Body image" (see Fig. 3).

Thus, by the sixth month of treatment, the patient achieved low SLE activity (SLEDAI-2K — 4 points) while on stable therapy with MP 4 mg/day, hydroxychloroquine 200 mg/day, MMF 1000 mg/day and AFM 300 mg (IV drip); and there was significant improvement of HRQoL over time. Due to this, a decision was made to perform surgery.

On 16 October 2023, the patient was admitted to traumatological and orthopedic department of V.A. Nasonova Research Institute of Rheumatology. Local status: impaired walking, limping on the left lower limb. Mild hypotrophy of the left thigh muscles. Restricted movements: 100° flexion, full extension, 10° abduction, 10° adduction, 20° external rotation, 5° internal rotation. No trophic or neurocirculatory disorders. Pelvic X-ray exam: both sacroiliac joints demonstrate quite well-defined smooth contours and have normal width; the joint spaces are visualized along their entire length; there are no signs of subchondral osteosclerosis. The left acetabulum appears dysplastic, shallow, covering 2/3 of the femoral head (Fig. 4, a); there is uneven narrowing of the hip joint spaces with the presence of pronounced osteosclerosis of the femoral heads and cystic lesions in them; the femoral heads are deformed, flattened and appear reduced in size. During the period of surgical treatment and rehabilitative care, MMF and AFM were discontinued.

On 17 October 2023, a total hip replacement of the left hip joint (Zimmer implant) was performed. Postoperative X-ray exam



	Physical health	Pain	Planning	Burden to others	Emotional health	Body image	Fatigue
Before therapy	65	58	41	58	62	65	56
After 6 months	97	100	56	100	100	92	100

Fig. 3. *Improvement of health related QoL during AFM therapy according to the Lupus-QoL questionnaire*

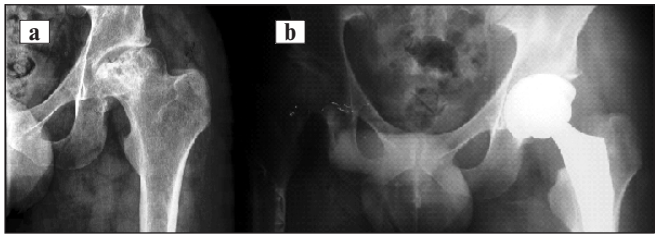


Fig. 4. *X-ray images of the left hip joint before (a) and after (b) total hip arthroplasty*

of the left hip joint (18 October 2023) (see Fig. 4, b): the soft tissues are intact, with small air inclusions in the outer regions; status post total replacement of the left hip joint; the cup of the prosthesis has a typical location in the acetabulum; the femoral component of the prosthesis is located centrally in the femoral medullary canal; the ratio of the prosthesis components is correct; there are no reactions of the adjacent bone tissue. There were no complications in the postoperative period. On 24 October 2023, the patient was discharged to continue therapy in the outpatient setting. Therapy with MMF 500 mg/day was restarted; and the administration of MP 2 mg/day, hydroxychloroquine 200 mg/day was continued.

At a follow-up visit to V.A. Nasonova Research Institute of Rheumatology on 19 December 2023, it was revealed that the patient had not been receiving AFM for three months; the last infusion was carried out in September 2023; the total duration of AFM therapy was 6 months. In the middle of December 2023, after being exposed to cold temperatures, the patient developed capillaritis and rash on his hands, and the immunological activity of his disease began to increase: anti-dsDNA — 800 IU/mL (reference range: 0–100 IU/mL). It was recommended to increase the dose of MP to 4 mg/day, the dose of hydroxychloroquine to 200 mg/day, and to restart therapy with AFM. On 23 January 2024, the patient was examined again at the Department of Outpatient Therapy, Clinical Laboratory Diagnostics and Medical Biochemistry of Yaroslavl State Medical University and at Yaroslavl Regional Clinical Hospital. Moderate capillaritis, rash on the hands and few skin lesions on the face were revealed. The patient reported significant improvement in his well-being and ability to work saying "...now I can squat and go faster; my body flexibility has increased; my sleep has improved".

It is planned to continue therapy with AFM and perform total hip replacement surgery of the right hip joint at V.A. Nasonova Research Institute of Rheumatology.

Discussion. Over the past years, modern drugs and therapeutic options for SLE patients have been introduced into clinical practice (in particular, the "treat-to-target" strategy). [13] Despite this, according to I. Z. Gaidukova et al., [14] in cohorts of SLE patients diagnosed between 2000 and 2009, and between 2010 and 2019, the number of patients, who did not achieve low disease activity or remission, remains virtually unchanged — 44.4 and 47.1% respectively. At the same time, 76% of patients constantly take CSs at doses exceeding 7.5 mg of prednisolone per day. There is also a high incidence of comorbidities, involvement of vital organs and systems as a result of persistent inflammation and the use of immunosuppressive therapy, especially CSs. Therefore, it is necessary to search for new approaches for the treatment of SLE in order to achieve the remission or minimal disease activity with or without low-dose CS therapy.

On 28 April 2021, an online meeting of the Expert Council on Rheumatic Diseases was held, where the application of AFM as a promising treatment for SLE was discussed. The experts concluded that patients without severe kidney and central nervous system damage, those with a relapsing disease course, joint and skin involvement, high immunological activity, in whom it is impossible to decrease the CS dosage can benefit the most from the use of this drug. [15]

In Russia, few cases describing successful use of AFM as part of the early access program have been reported in patients with SLE resistant to traditional treatment regimens, including multiple lines of cytotoxic drugs or biological therapy agents. [16,17] AFM has been shown to have high efficacy and safety in the treatment of SLE with active lesions of the skin, mucous membranes and joints. AFM provides rapid improvement in the form of regression of cutaneous and articular manifestations with normalization of immunological parameters, which allows for a reduction in CS dosage, and potentially their discontinuation, leading to clinical and laboratory remission.

T.M. Reshetnyak et al. [18] presented the results of 12-month follow-up of 21 patients with SLE treated with AFM. According to the authors, indications for prescribing the drug include active SLE according to SLEDAI-2K and/or CLASI with predominant involvement of the skin and its appendages and development of polyarthritis with immunological abnormalities, intolerance/ineffectiveness of prior standard of care as well as biological therapy (rituximab, belimumab, dual anti-B-cell therapy), as well as the inability to achieve low maintenance doses of oral CSs.

This article describes a patient who was born and lived in Kazakhstan and then moved permanently to Uglich town of Yaroslavl region. However, the patient is not an ethnic Kazakh or a native of the Yaroslavl region - the regions which, according to one study, are characterized by a high prevalence and incidence of

SLE. [19] The patient was prescribed AFM. He had previously received 21 courses of pulse therapy with 6-MP and CP for lupus nephritis with positive effect, however, while on therapy with CS, he developed bilateral femoral head avascular necrosis. As in previous case reports, this patient had refractory disease with recurrent cutaneous and articular manifestations and high immunological activity. After the AFM administration, there was rapid (as early as one week later) regression of skin lesions. This effect was maintained for 9 months, including 3 months after the discontinuation of the drug. Three months after the AFM therapy initiation, the general disease activity score was significantly lower, and by the 6th month, clinical manifestations of SLE were completely reversed. At the same time, there was a normalization of a number of laboratory parameters, a decrease in the ANF titer and anti-dsDNA concentration.

Significant improvement of the immunoinflammatory process while on therapy with AFM and reduction of CS dosage allowed for successful total replacement of the left hip joint after six months of therapy, which makes this case report different from other reported clinical cases. Earlier, Ya. A. Leineman et al. [16] indicated an increase in the incidence of infectious complications (including herpes virus infections) in patients receiving AFM. However, in our case, no infections were registered even in the most critical early postoperative period, and the low LSE activity was maintained for four months after the last AFM injection and after total hip replacement surgery,

Conclusion. Thus, AFM is the first drug to target and inhibit type I interferon, that has been shown to be effective in treating the torpid cutaneous and articular disease manifestations associated with high levels of laboratory markers of the SLE activity. AFM allows for a rapid achievement of low disease activity without increasing the dose of CSs, significantly improves patients' quality of life, and can even prepare them for major surgeries without exacerbating the underlying condition.

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