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Systemic lupus erythematosus treatment strategies**

Leczenie tocznia rumieniowatego układowego

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S u m m a r y

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by excess: autoantibody production; cytokine production; complement activation and diverse clinical consequences of these immunological abnormalities. The nature of the SLE is very heterogeneous. In the course of the disease a clinical pattern of flares and remissions can be observed. The management of SLE depends on disease, clinical manifestations; major organ involvement and comorbidities due to the disease or its treatment. The treatment of SLE varies according to an individual and disease severity. It is important to maintain an appropriate level of therapy to control or halt inflammatory disease activity while minimizing side effects and risk of infection and to prevent further major organ damage. Treatment plans are tailored to the individual's needs and may change over time, depending on disease activity, different types of drugs are used. Corticosteroids can be applied on the skin in creams, while for people with joint or chest pain and fever non-steroidal anti-inflammatory drugs and other types of drugs to control pain, swelling and fever may be used. Antimalarials are drugs commonly used to treat lupus fatigue, joint pain, skin rashes and inflammation of the lungs. Continuous treatment with antimalarials may prevent flares from recurring. Coritcosteroids are the mainstay of SLE therapy. Cytotoxic agents suppress the immune system and are frequently used in SLE. Azathioprine, cyclofosphamide, mycophenolate mofetil, cyclosporine, methotrexate are most useful especially for patients whose kidneys and central nervous system are affected. In severe life-threatening type of the disease intravenous gammaglobulin, plasmapheresis and biologics may be considered as the therapy. In patients with secondary antiphospholipid syndrome a long-term treatment with low-dose aspirin, heparin or oral anticoagulants is recommended. Prophylaxis of cardio-vascular disease and osteoporosis is recommended for all patients with SLE.

Key words: systemic lupus erythematosus, activity, treatment, biologics

S t r e s z c z e n i e

Toczeń rumieniowaty układowy (SLE) jest przewlekłą autoimmunizacyjną chorobą zapalną, charakteryzującą się nadmierną produkcją autoprzeciwciał i cytokin oraz aktywacją dopełniacza i wynikających z tego konsekwencji klinicznych. Obrazy kliniczne choroby mogą być różnorodne. W przebiegu SLE występują okresy zaostrzeń i remisji. Leczenie choroby zależy od jej postaci klinicznej, aktywności, stopnia zajęcia narządów wewnętrznych, chorób towarzyszących, występujących powikłań polekowych. Ma na celu właściwe kontrolowanie aktywności zapalnej dla zapobieżenia trwałym uszkodzeniom narządowym. Jednocześnie, istotne jest minimalizowanie działań niepożądanych leków i ryzyka wtórnych infekcji. W leczeniu SLE zależnie od aktywności choroby stosowane są różne grupy leków. Na skórę stosowne są preparaty zawierające glukokortykosteroidy działające miejscowo; objawowo podawane są leki przeciwbólowe oraz niesteroidowe leki przeciwzapalne. Leki antymalaryczne są lekami często stosowanymi w leczeniu SLE. Są najczęściej używane do leczenia objawów stawowych, zmian skórnych, uporczywego zmęczenia i zmian zapalnych w płucach. Potwierdzono, że przewlekłe stosowanie leków antymalarycznych zapobiega zaostrzeniom choroby, w tym również zaostrzeniem toczniowego zapalenia nerek. Glukokortykosteroidy są lekami podstawowymi w leczeniu SLE. Leki immunosupresyjne i cytostatyczne blokują funkcję układu immunologicznego i dlatego są chętnie używane w leczeniu SLE. Najczęściej z tych grup leków używane są (szczególnie przy zajęciu w przebiegu choroby nerek i ośrodkowego układu nerwowego) azatiopryna, cyklofosfamid, mykofenolat mofetylu, cyklosporyna A, metotreksat. W postaciach SLE, w których dochodzi do bezpośredniego zagrożenia życia i funkcji narządów stosuje się wlewy dożylne immunoglobulin, plazmaferezy, w wybranych przypadkach leki biologiczne. Przy rozwoju w przebiegu SLE wtórnego zespołu antyfosfolipidowego należy do stosowanego leczenia immunosupresyjnego dołączyć leczenie przeciwkrzepliwe. U niektórych chorych z dominującymi w obrazie chorobowym powikłaniami zakrzepowymi może to być podstawowe leczenie SLE. U wszystkich chorych należy stosować profilaktykę powikłań sercowo-naczyniowych oraz osteoporozy.

Słowa kluczowe: toczeń rumieniowaty układowy, aktywność, leczenie, leki biologiczne

**The paper dedicated to Professor Eugene J. Kucharz with greetings from Lublin on his sixtieth brithday.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multifactorial etiology and diverse clinical symptoms and signs which depend on the involvement of many tissues and organs. In practice, every tissue may be affected by the disease. In the course of the disease a broad spectrum of both clinical and laboratory signs is established. The disease is most often manifested by symptoms and signs of the skin and in the joints as well as by cytopenia (1-3).

The main factors in the pathogenesis of SLE include:

- abnormal immune response of humoral nature;
- elevated production of antibodies to multiple autoantigens;
- hypocomplementemia – and the correlated abnormal phagocytosis and elimination of apoptotic cells and apoptotic bodies;
- excessive activation of B and T lymphocytes;
- imbalance in cytokine synthesis.

Pathogenic antibodies activity is the primary cause of tissue damage in the course of SLE. The production of antibodies increases evidently as a result of many stimulating factors affecting human immune system. The treatment of SLE may be aimed at many functional elements of the immune system. Blocking them off with drugs reduces the impact of pathogenic antibodies (1-3).

Modern methods of the individualized SLE management should concern separate stages of the disease process; they should take into account the disease activity and the risk of internal organ damage. On planning the treatment of SLE, it is necessary to consider comorbidities due to the disease or side effects of previously administered drugs. Long-term treatment of SLE has to take into account the patient's quality of life and their personal and professional life objectives.

MODERN RULES OF TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS – RECOMMENDATIONS OF EULAR OF 2008

In 2008 EULAR (European League Against Rheumatism) published its recommendations for the management of SLE (4). The issues of diagnosis, prognosis, monitoring and treatment of SLE were addressed. As a result, twelve recommendations were developed, concerning:

- general management of SLE (5 recommendations);
- lupus nephritis (3 recommendations);
- neuropsychiatric lupus (2 recommendations);
- pregnancy in lupus (1 recommendation);
- anti-phospholipid syndrome (1 recommendation).

Recently, EULAR's recommendations for monitoring of disease activity, concerning general signs and symptoms and changes in systems and organs, have been presented (5).

GENERAL RECOMMENDATIONS FOR MANAGEMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS

Those recommendations include the assessment of data on disease prognosis and progression (4). In prognosis, the new emerging clinical symptoms and signs – such as rashes, arthritis, serositis, neurological manifestations, seizures – should be considered. The laboratory (CBC, serum creatinine, proteinuria, urinary sediment) and immunological tests (complement concentration, marker antibody titer) provide essential information on the involvement of major organs and prognosis of the course of the disease. The assessment of the renal and nervous system involvement should be complemented by imaging (brain MRI) and renal biopsy. In the evaluation of prognosis for the progression and the appropriate treatment of the disease, the comorbidities should be considered. These comorbidities include infections, hypertension, accelerated atherosclerosis and its consequences, osteoporosis, dyslipidemias, avascular necrosis and the increased risk of malignancy.

General recommendations represent the opinion of EULAR on the treatment of SLE patients without the involvement of major organs (4). In such cases, patients usually have cutaneous lesions, motor system disorders, serositis and general signs such as persistent fatigue and mood changes (3, 4). Non-steroidal anti-inflammatory drugs, analgesics, antimalarials such as hydroxyl-chloroquine, chloroquine and quinacrine play an important role in the treatment of those patients. Antimalarials make their 'comeback' in the treatment of SLE. They are considered very effective and low toxic in the less active course of the disease and in the maintenance therapy following the induction therapy (4, 6). If it proves to be insufficient, glucocorticosteroids are administered orally or in the form of ointments. In some cases, androgenic drugs such as dehydroepiandrostenone (DHEA) are prescribed, especially to reduce a long-term corticotherapy. In patients non-responsive to the treatment with the use of symptomatic drugs and glucocorticosteroids aimed at suppressing general symptoms and motor system disorders, and in patients not being able to tolerate a long-term treatment with glucocorticosteroids due to their adverse effects, immunosuppressive agents such as azathioprine, methotrexate and leflunomide should be considered (4, 6).

LUPUS NEPHRITIS – CONSECUTIVE IMMUNOSUPPRESSIVE THERAPY OF LUPUS NEPHRITIS

Renal involvement is diagnosed in 29-75% of SLE patients, most of whom manifest first signs of lupus nephritis at the early stage of the disease. EULAR's recommendations of 2008 (4) focused on diagnosis, monitoring and treatment as well as the management of the end-stage renal disease. Marker antibodies whose titer rises significantly in lupus nephritis are **anti-dsDNA** and **anti-C1q** which has been recently added to routine laboratory tests. The most common

type of renal damage in SLE is glomerulonephritis, caused by the presence of immune complexes. The main signs of this type of nephritis are proteinuria, abnormal urinary sediment, hypertension and glomerular filtration impairment.

Before the determination of appropriate treatment of lupus nephritis, it is crucial to evaluate the glomerular filtration and the stage of chronic renal disease, establish the possible nephritic and nephrotic syndromes, and investigate the moderately intense urine changes with or without hypertension. It is of great importance to assess the lupus nephritis activity diagnosed in a patient. **It is obvious that the final diagnosis should be confirmed by histopathological examination and renal biopsy.** It allows for assigning the lupus nephritis category according to the classification of the World Health Organization (WHO); what is more, the disease activity and the progression of irreversible changes (sclerosis) may also be evaluated (7, 8). Proliferative types of lupus nephritis (class III and IV of lupus nephritis according to WHO) are the most severe and lead to end-stage renal disease in 25% of patients. It is known that 13% of SLE and lupus nephritis patients die from complications of lupus and its treatment, especially due to infections. For this reason, treatment of severe lupus nephritis is a great challenge and requires careful consideration of benefits of the intensive immunosuppressive therapy and the accompanying risk of its adverse effects. **There are lupus nephritis treatment strategies, established on the basis of WHO classification of changes:** for mild lupus nephritis (class I and II), for moderate lupus nephritis (class III), for moderate and severe lupus nephritis (focal proliferative glomerulonephritis – class III; diffuse proliferative and membranous-diffuse glomerulonephritis – class IV), and for changes of class V (membranous nephritis).

The evaluation of histopathological changes and the disease activity allows for determining whether SLE patients are in a life-threatening condition or in danger of renal failure. In those cases, classes III, IV, and V of histopathological changes are assigned. The treatment of acute stage of lupus nephritis should be aimed at a possibly quick remission of the disease and thus the reduction of organ damage due to acute inflammation. At this time, the induction therapy is applied, according to the severity of disease (8-16). If renal disease exacerbates, it is necessary to intensify the therapy and to proceed from the lower to the higher class treatment strategy. The main aim of the lupus nephritis treatment is to quickly induce remission and to maintain it, which reduces the risk of progressive renal damage.

In lupus nephritis patients with class-I and class-II morphological changes according to WHO, with proteinuria < 1 g/24 h and a regular glomerular filtration, treatment should be aimed at extranephric signs of SLE – usually it involves prednisone administered orally and antimalarials (it has been established that long-term use of hydroxyl-chloroquine reduces the frequency of flares and aggravation of lupus nephritis (6, 8, 10, 16)).

The treatment of active lupus nephritis usually starts with a period of intensive immunosuppressive therapy – **induction therapy**. Then, a period of less intensive immunosuppressive therapy follows – **maintenance therapy** (tab. 1).

Table 1. Scheme of consecutive immunosuppressive therapy of lupus nephritis.

Induction therapy	**High doses of glucocorticosteroids Prednisone + cyklophosphamide or mycophenolate mofetil, cyclosporine A In some cases rituximab**	**Reduction of inflammatory damage**
↓	↓	↓
Maintenance therapy	Prednisone + azathioprine or mycophenolate mofetil or methotrexate, hydroxychloroquine (chloroquine)	Prevention of disease flares Reduction of adverse effects

Induction therapy usually begins with high doses of glucocorticosteroids, administered intravenously (0.5-1.0 g for 3 consecutive days); intravenous infusions may be repeated every 4-6 weeks if necessary; in the meantime prednisone is administered orally (20-30g/day). In class-III lupus nephritis according to WHO, treatment may begin with an oral administration of prednisone in dose of 1 mg/kg of body mass/24 h for 2 weeks, then progressively reduced every 2 weeks until it reaches the maintenance dose of 5-10 mg/24 h. In high disease activity with bad prognosis and a decrease in glomerular filtration from the onset of the disease, the originally high doses of glucocarticosteroids are combined with other immunosuppressive drugs. If the patient did not receive an initial loading dose of cyclophosphamide (over 150 mg/kg of body mass), it is recommended to include the therapy of cyclophospamide pulses administered every 3-4 weeks (750 mg/sq meter in regular renal function, or 500 mg/sq meter in lower glomerular filtration). Cyclophospamide therapy in pulse doses continues for 6 months, repeated every month, and then for two years, repeated every three months (6, 8-10).

High-dose cyclophospamide therapy, introduced into the lupus nephritis treatment in 1986, has revolutionized the outcome of the severe lupus nephritis treatment; it is, however, associated with many adverse effects (hemorrhagic cystitis, myelosuppression, gonad damage, infections). Intravenous cyclophosphamide is the only agent which has been proved to reduce the number of end-stage renal failure in lupus. In 2002 Houssiau F et al. (11) proposed alternative cyclophosphamide administration strategy (Euro-Lupus), associated with a smaller number of adverse effects, which is used in the lupus nephritis induction therapy more and

more often. In this strategy, cyclophosphamide is administered intravenously in regular doses of 500 mg six times every two weeks – in total 3 g – followed by oral administration of azathioprine in doses of 1-2 mg/kg of body mass/24 h.

The search for new, safer forms of severe lupus nephritis types is still ongoing. New therapeutic opportunities has appeared after mycophenolate mofetil demonstrated immunosuppressive efficacy (12-15). This agent inhibits guanine purine synthesis which results in the inhibition of T and B lymphocyte proliferation. The drug is administered in a gradually increased doses up to 3g/24h. Many studies have proved that mycophenolate mofetil may be as effective in induction therapy as cyclophosphamide. In maintenance therapy it is an effective drug, safer than cyclophosphamide (13-15).

If induction therapy is ineffective, various alternative therapies are applied: intravenous immunoglobulin, plasmapheresis. Recently, there have been instances of patients, non-responsive to classical methods of induction, demonstrating a response to rituximab, an antibody directed against CD20 (17).

Maintenance therapy should be continued for a period of at least one year after the remission of renal signs. In maintenance therapy small doses of prednisone (5-10 mg), combined with one of the immunosuppressive agents such as azathiopryne, mycophenolate mofetil or methotrexate, are administered.

In some SLE patients, especially those with cytopenia, cyclosporine A (3-5 mg/kg/24 h) is used as the mainstay of the immunosuppressive therapy, administered orally in two equal doses. It may be effective in induction and maintenance therapy. However, its adverse effects such as higher blood pressure or inhibition of glomerular filtration should be taken into consideration (18).

SLE patients should always be provided with a standard kidney and heart protective therapy along with immunosuppressive therapy; standard therapy includes controlling blood pressure with the use of angiotensin-converting enzyme inhibitors, treating lipid disorders, and controlling glycaemia.

One of the essential problems in long-term SLE treatment is to find SLE and lupus nephritis patients who simultaneously suffer from secondary antiphospholipid syndrome, and to determine whether there are changes in their kidneys resulting from thrombotic microangiopathy associated with SAPS, secondary antiphospholipid syndrome present in about 20% of lupus nephritis patients, or from the presence of antiphospholipid antibodies of high titers. Such patients need to be provided with a full anticoagulative therapy (1, 6, 8, 10).

SLE patients with end-stage renal disease are provided with a renal replacement therapy (peritoneal dialysis, hemodialysis), and are qualified for renal transplantation.

The disease "burns out" in the majority of patients as the renal failure advances, and the patients do not require intensive immunosuppressive therapy. In some patients, especially young women, the disease may still be active and thus they may require more intensive immunosuppressive therapy. It may happen that the serologic activity of the disease in patients with advanced renal disease is not accompanied by the clinical activity.

In recent years, the prognosis for SLE patients in the period of advanced chronic renal failure has significantly improved. The disease activity lessens in this period in the majority of patients. The survival rate of SLE patients provided with a renal replacement therapy is similar to other groups of patients undergoing dialysis.

The prognosis for patients after transplantation seems to be slightly worse than for non-SLE patients due to the risk of lupus nephritis flare and the impact of antiphospholipid antibodies on complications (8, 19).

NEUROPSYCHIATRIC LUPUS

In SLE patients with central and peripheral nervous systems manifestations and psychiatric symptoms, special attention should be drawn to attempts at determining the etiology of those changes – whether the changes are resulting from lupus or secondary antiphospholipid syndrome (4, 6, 20, 21). EULAR has recently published its recommendations for management of SLE with neuropsychiatric manifestations. In accordance with the severity of signs and their etiology, appropriate treatment is chosen; it might be symptomatic treatment (depressive and psychotic signs), immunosuppressive treatment if meningoencephalitis is suspected, or anticoagulative treatment if complications of antiphospholipid syndrome are suspected. In the most severe cases, it is necessary to administer megadoses of glucocorticosteroids, cyclophosphamide, and in some cases biologics inhibiting B cells (6, 20, 21).

SLE TREATMENT WITH ANTIPHOSPHOLIPID ANTIBODIES, WITH SECONDARY ANTIPHOSPHOLIPID SYNDROME AND CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

Petri M (22) has published the results of studies investigating the relation between the individual antiphospholipid antibodies and the type of thrombotic complications in SLE patients. Anticardiolipin antibodies were found in 47.4% of patients, lupus coagulant – in 25.8%, antibodies to β2-GPI – in 32.5%. In SLE patients with lupus anticoagulant the risk of developing deep-vein thrombosis and/or pulmonary embolism was 50% higher during twenty years after the onset of the disease. Various antiphospholipid antibodies can play various roles in SLE patients with thrombosis. Patients with lupus anticoagulant are at the highest risk of developing venous and arterial thrombosis. Only the presence of lupus anticoagulant constitutes a significant risk of myocardial infarction in SLE patients (22).

Hughes (23) gives the **following recommendations for pregnant women**, implemented in his *Maternity clinic for SLE patients of St. Thomas Hospital*:

1. In patients with antiphospholipid antibodies but without thrombosis or pregnancy complications recorded in their medical history it is recommended to administer 75 mg of aspirin per day throughout the pregnancy.
2. In patients with antiphospholipid antibodies and thrombosis or recurrent miscarriages recorded in their medical history it is recommended to administer subcutaneous low-molecular-weight heparyn (dalteparin) (Fragmin) in dose of 5000 units/day or enoxaparin (Clexane) in dose of 40 mg/day throughout the pregnancy, together with small doses of aspirin.
3. Patients who underwent miscarriage, with a few antiphospholipid antibodies, are prescribed higher doses of heparin, especially in the third trimester of pregnancy.

About 1% of antiphospholipid syndrome patients develop catastrophic antiphospholipid syndrome. About 40% of CAPS cases occur in SLE (24).

The death rate in catastrophic antiphospholipid syndrome is estimated at 50% of all cases; recently is has been reduced to 30% due to treatments according to new recommendations (25).

Early diagnosis and aggressive therapy are the foundation of appropriate treatment. The registered cases of antiphospholipid syndrome patients have been analyzed, which resulted in a new treatment startegy in catastrophic antiphospholipid syndrome. It refers to the appropriately conducted prevention and the appropriately targeted therapy.

APPROPRIATE PREVENTION OF CASTASTROPHIC ANTIPHOSPHOLIPID SYNDROME

1. All infections in antiphospholipid syndrome patients, even the minor ones, should be treated effectively.
2. Surgeries (even the small ones) in antiphospholipid syndrome patients should be performed with the use of parenteral anticoagulation instead of the oral one.
3. In the postnatal period, parenteral anticoagulation (subcutaneous heparin) should be continued for a period of at least 6 weeks.

TARGETED THERAPY IN CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME

1. **Anticoagulation:** intravenous heparin for 7-10 days, then oral anticoagulant with INR of at least 3.

2. **Glucocorticosteroids:** to stop the excessive release of cytokines and SIRS mediators and to prevent antiphospholipid antibodies-mediated thrombosis, all catastrophy antiphospholipid syndrome patients should be administered glucocorticosteroids. They should be used for at least 3 days, but depending on the patient's response this therapy might need to be prolonged.

3. **Plasmapheresis** is the treatment of choice in patients with thrombocytopenic purpura. The way it acts in catastrophic antiphospholipid syndrome has not been fully explained; the removal of pathogenic antiphospholipid antibodies, of cytokines IL-1 and IL-6, of TNF-α and of complement is taken into consideration.

4. **Intravenous immunoglobulin:** the recommended dose is 0,4 g/day/kg of body mass for 4-5 days. Intravenous immunoglobulin may be beneficial especially for patients with severe thrombocytopenia, and may reduce the synthesis of antibodies and increase the catabolism of circulating immunoglobulin.

5. **Cyclophosphamide:** multifactorial analysis of catastrophic antiphospholipid syndrome patients data indicates that cyclophosphamide is effective and should be used in catastrophic antiphospholipid syndrome – SLE patients, but not in patients with primary antiphospholipid syndrome.

6. **Rituximab:** monoclonal antibody to CD-20 was effective in treating catastrophic antiphospholipid syndrome patients non-responsive to other methods, with severe thrombocytopenia and autoimmune hemolytic anemia.

7. **Fibrinolytic therapy:** with the aid of streptokinase, urokinase, tissue plasminogen activator, is used in exceptional situations in patients with severe catastrophic antiphospholipid syndrome. It is, however, associated with significant severe hemorrhagic complications.

8. **Symptomatic therapy:** many patients with multiple organ dysfunction syndrome require intensive care at the time of acute disease, with possible mechanical ventilation, renal replacement treatment and acute hypertension treatment.

PREGNANCY IN LUPUS

The management of a pregnant SLE patient is a challenge for the practicing physician. It is necessary to balance the benefits of treatment to a mother and the adverse effects of drugs on a child. Most commonly the treatment from before the pregnancy is continued in order to reduce the risk of aggravation of the disease. Thus, in the pregestational period it is recommended to prescribe drugs which are not counter-indicated during pregnancy. Before getting pregnant, the woman should take folic acid in doses of 0.4 mg/24 h to reduce the risk of neurological damage for fetus. Nonsteroidal anti-inflammatory drugs can be taken safely in the second trimester. Acetominophen is considered to be safe in pregnancy to alleviate pain. Low-dose aspirin is safe for patients with antiphospholipid syndrome during pregnancy, but patients should come off it before childbirth due to the risk of hemorrhage. Heparin and low-molecular-weight heparin have proved to be safe during pregnancy. Glucocorticosteroids, the mainstay of SLE treatment, may be used during pregnancy. In the placenta, 11β-hydroxysteroid dehydrogenase (11β-HSD) inactivates prednisone and prednisolon so that only about 10% is transmitted to the fetus. Betamethasone is not metabolized by 11β-HSD and is easily

transmitted through placenta, so it might be helpful to treat the fetus with neonatal lupus or to accelerate the fetal maturity in preterm labor. Prednisone taken during pregnancy may increase the risk of hypertension, diabetes mellitus and pre-eclamptic condition in mothers. The preventive use of prednisone is not indicated during pregnancy due to its adverse effects, whereas if SLE activity increases it may be necessary to indicate a higher pulsed-dose intravenously or a higher dose orally.

SLE women often become pregnant when treated with hydroxychloroquine. Coming off this drug is associated with the high risk of disease exacerbation, especially skin and joint symptoms. The drug can be used safely during pregnancy. However, chloroquine rises more doubts. Azathioprine has been proved to be safe in many trials on patients taking the drug after renal transplantation. The occurrence of congenial defects has not been detected during the use of the drug. Azathioprine may be included in maintenance therapy, started before pregnancy, or may be indicated during pregnancy if SLE exacerbates. Cyclophosphamide, methotrexate and mycophenolate mofetil are counter-indicated during pregnancy due to the risk of birth defects (1, 6, 26).

ADJUNCT-THERAPY IN SYSTEMIC LUPUS ERYTHEMATOSUS

While treating with cyclophosphamide, the therapy protecting gonads consists in administering intramuscular leuprolide (antagonist of gonadotropin-releasing hormones) to women in doses of 3.75 mg every 4-6 weeks, and in administering intramuscular testosterone to men in dose of 200 mg every 2 weeks. This therapy should start one month before administering cyclophosphamide and be continued when the patient is treated with cyclophosphamide (27).

On occurrence of hypertension, dyslipidemia, renal involvement in the course of the disease, chronic treatment of SLE should be complemented with nephro- and cardioprotection with aid of angiotensin-converting enzyme inhibitor and statins. It is also necessary to apply chronic treatment to prevent the development of steroid-induced osteoporosis, by supplementary use of vitamin D and calcium, and – if the woman's kidneys are functioning properly after the menopause – by use of bisphosphonates. To reduce the homocysteine concentration, folic acid in doses of 5 mg/day is indicated, and the preventive measures to avoid obesity as well as tobacco cessation are recommended (1, 6, 10).

NOVEL THERAPIES – BIOLOGICS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Even though we dispose of a wide range of drugs to treat SLE, there are continuous searches for newer, safer and more effective therapies. It may be assumed that the ideal treatment of SLE should reduce the SLE-related death rate, reduce the incidence rate of end-stage renal failure in SLE patients, give early response and induce quick remission, prevent flares, be associated with a minimum number of adverse effects, not cause infertility, be effective in all ethnic groups, and be widely available due to low cost.

Biologics, proved to be effective in treating rheumatoid arthritis, are now the subject of research in SLE. Many clinical trials are being conducted, aimed at determining the efficacy of drugs blocking various elements of the immune system involved in SLE pathogenesis. SLE patients have undergone clinical trials with monoclonal antibodies blocking T lymphocytes (e.g. anti-CD40L monoclonal antibodies, or abatacept – CLTA4 – Ig), the B-lymphocyte activity (e.g. rituximab – anti-CD20, epratuzumab – anti-CD22 monoclonal antibodies, belimumab – anti-BLyS monoclonal antibodies), the synthesis of anti-nDNA antibodies (abetimus sodium – LJP 394), and the activation of cytokines and complement elements (monoclonal antibodies to IL-6 receptor, to IL-10; epratuzumab – anti-C5 monoclonal antibodies) (1, 6).

Observations of each drug's efficacy are made on the basis of investigating the efficacy of drugs in patients who are very resistant to the registered methods of SLE treatment. A big amount of clinical data refers to instances of the use of rituximab in LN patients with CNS involvement and CAPS (1, 6, 17, 25). The registration of belimumab, a human monoclonal antibody that inhibits B-lymphocyte stimulator (BLyS), rises huge hopes. Studies of the II and III phase have proved the efficacy of belimumab. During treatment, the disease activity was significantly reduced, while the disease exacerbation was less frequent, with the safety profile of the drug remaining at the same level (1, 6).

SUMMARY

Systemic lupus erythematosus treatment regimen

With EULAR's recommendations as a starting point, with consideration of the available literature and from our own experience in clinical practice, we present the regimen of SLE treatment (fig. 1).

Stage 1

Before deciding on treatment of a given patient, the following should be evaluated (with the use of many diagnostic methods):

- the form of the disease;
- the involvement of internal organs and how advanced this involvement is;
- the risk of organ failures;
- the life-threatening risk;

The disease activity may be classified according to various classifications of disease activity. In Poland, the most common classification is SLEDAI (Systemic Lupus Erythematosus Diseases Activity Index).

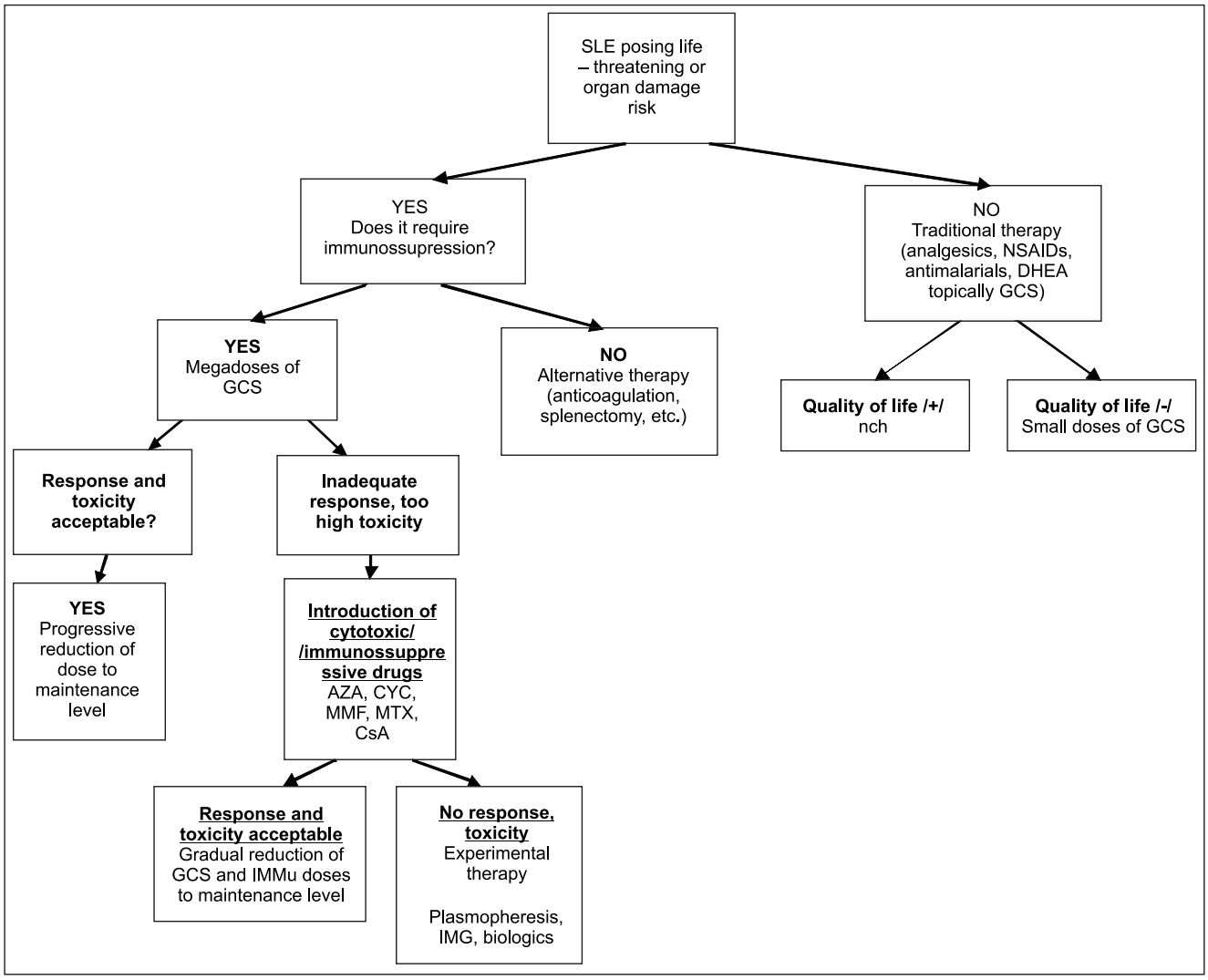

Fig. 1. Regimen of diagnostic strategy in systemic lupus erythematosus.
SLE – systemic lupus erythematosus; NSAIDs – non-steroid anti-inflammatory drugs; GCS – glucocorticosteroids; nch – no change; AZA – azathioprine; CYC – cyklophosphamid, MMF – mycophenolate mofetil; Mtx – methotrexate; CsA cyclosporine A; IMMu – immunosuppression; IMG – immunoglobulins iv.

Stage 2

After conducting all diagnostic tests, we know whether a given case of SLE is life-threatening or presents a risk of internal organs damage or not. **If the answer is negative** – in such cases mostly non-specific complaints are reported, concerning musculoskeletal system, skin rashes, and general signs: fatigue, anxiety, exhaustion – we apply a traditional therapy, using analgesics, non-steroid anti-inflammatory drugs, immunomodulatory drugs, and above all the antimalarials and dehydroepiandrosterone (DHEA), prolactin-blocking drugs, and ointments with glucocorticosteroids as well as sun cream topically on the skin. If such therapy suffices to alleviate symptoms and signs and maintain the appropriate quality of live, it is satisfactory. If the quality of life with those complaints is insufficient, low-dose oral glucocorticosteroids may be prescribed.

Positive answer to question whether a given case of SLE is life-threatening or presents a risk of internal organs damage obliges to apply induction therapy. It is necessary to establish whether the risk of internal organs damage is related to the autoimmune inflammation or to the thrombosis associated with secondary antiphospholipid syndrome. If we deal with the former, intensive immunosuppressive therapy is indicated, whereas if we deal with the latter, systemic anticoagulation with milder immunosuppressive therapy is recommended.

While treating an intense autoimmune inflammation, we usually start with megadoses of methylprednisolone intravenously in doses of 1000 mg for 3 consecutive days. Some regimens suggest an intravenous dose of 500 mg for 3 consecutive days. The therapy is continued by administration of oral medium-dose prednisone or methylprednisone. If the patient's response is adequate and the toxicity of drugs is well tolerated, the megadose of glucocorticosteroid could be repeated after a month and then gradually reduced until it reaches the maintenance level. If the patient's response is inadequate or the toxicity is too high, cytotoxic and im-

munosuppressive agents (cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosphorin, methotrexate) are included in the therapy. When the patient's response is satisfactory and the toxicity is tolerated, the doses of glucocorticosteroids and immunosuppressive drugs are gradually reduced to the maintenance dose.

If positive response is absent or the toxicity is too high, experimental therapies may be applied in the most severe clinical conditions, in which intravenous immunoglobulin, plasmapheresis or biologics are used. In some exceptional clinical conditions (posing a direct life-threatening risk), those experimental therapies should be introduced very quickly. These conditions include CAPS, severe thrombocytopenia, renal involvement with fast loss of renal function, severe hemolytic anemia, and severe CNS involvement in the course of the disease.

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