REVIEW ARTICLE

# New treatment strategy including biological agents in patients with systemic lupus erythematosus

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**KEY WORDS**

antimalarial drugs, biological therapy, immunosuppressive therapy, new treatment strategy, systemic lupus erythematosus

**ABSTRACT**

Systemic lupus erythematosus (SLE) is a heterogeneous disease, in which B lymphocyte activation and chronic inflammation play the key role. Both the disease itself and its treatment cause damage to multiple organs and systems. So far, despite intensive treatment, disease remission has been achieved in few patients, and the ratio of organ complications has increased significantly. This is caused by a long-term glucocorticoid therapy with a relatively rare use of immunosuppressive drugs. With a new treatment strategy and modern immunotherapy, it is possible to reduce the mortality rate, limit multiple-organ damage, thereby significantly improving the quality of life and prognosis of patients with SLE. The "treat-to-target" strategy enables targeted treatment resulting in a long-term symptom remission. It is based on an intensive immunosuppressive treatment with simultaneous reduction of glucocorticoid doses, and limiting their use solely to exacerbations in disease activity. The current idea for treatment is also the conscious use of the beneficial potential of background SLE treatment including antimalarial agents and standard immunosuppressive therapy. With the first biological agent approved for SLE treatment, the new age of therapy has dawned. Biologics offer new prospects and possibilities to induce clinical and immunological remission of SLE.

**Introduction** Systemic lupus erythematosus (SLE) is one of the most interesting and heterogeneous inflammatory diseases, diagnosed and treated within the field of clinical rheumatology. It is associated with multiple system and organ damage affecting all cells in the body and has an autoimmune background. The variability of symptoms is reflected by the lack of clear-cut classification criteria for SLE. For many years, its treatment has been based more on practical experience than on reliable scientific data and generally accepted uniform standards. Thus, daily decisions on treatment options are often challenging.

There are more and more reliable data from a number of clinical studies and long-term follow-ups of patients with SLE. Therefore, the view on its therapy has been changing. Its aim is not only to reduce or eliminate disease symptoms and activity but to induce long-term remission, thus limiting organ complications caused by the disease itself and applied treatment. Currently, the main objective of therapy is to reduce the severity of exacerbations and prolong the periods between successive episodes. At the same time, the therapy aims at reducing the demand for glucocorticoids (GC), so far considered as a standard background treatment. It was proved, however, that prolonged GC use is the main cause of complications and irreversible organ damage. The SLE treatment based on a long-term use of high-dose GCs and available immunosuppressive and antimalarial drugs has not produced desirable effects. Nonetheless, recent years have not only brought a new strategy and treatment opportunities but also disclosed a considerable needs for the best therapy.

Currently, most patients are characterized by moderate or high disease activity. It is independent of its duration and methods used for the assessment of disease activity. In the course of SLE,

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there is a high risk of successive flare-ups. Another problem is poor long-term prognosis. A decreased quality of life of patients with SLE compared with the healthy population results not only from multiple-organ symptoms of the disease but also from psychological and social factors. This is mainly the result of a chronic use of highly toxic immunosuppressive drugs, particularly GCs. Only half of the patients with moderate and severe SLE are fully satisfied with treatment results, while, paradoxically, rheumatologists have shared the opinion for many years that the effectiveness of the standard therapy is satisfactory. Possibly, this opinion results from therapeutic successes and, after all, a significant reduction in the mortality of patients observed in recent years. Although the overall mortality rate is high (in young patients aged between 16 and 24 years, it is more than 19-fold higher than in the healthy population), during the last 4 years, the average survival increased to 15 years from diagnosis. Currently, the majority of patients (79%) survive for over 20 years from diagnosis. On the other hand, data from various reports show that reduced mortality is accompanied by an increasing number of patients in whom irreversible organ changes significantly worsen the quality of life and enhance the risk of cardiovascular and other diseases.[1,2]

At the current state of knowledge based on evidence-based medicine (EBM), the available therapeutic recommendations are still suboptimal because their strength is insufficient as evidenced by few strong recommendations – 1A and 1B. Only 4 of 26 available recommendations are classified 1A or 1B. This group includes the following recommendations: use of GCs in SLE (1A); administration of mycophenolate mofetil (MMF), cyclophosphamide, angiotensin II inhibitors, and angiotensin II receptor antagonists not recommended in pregnant SLE patients (1A); induction of lupus nephritis (LN) treatment with cyclophosphamide (1B) or MMF (1B). The strength of 15 other recommendations is classified only as 2D. Moreover, 2 clinical studies that investigated the use of rituximab and abatacept have been criticized for violating the principles of EBM.[3-5] However, it should be highlighted that long clinical experience and data from patient registries and numerous clinical studies on biological agents, biomarkers, and stem cells have led to the development of new treatment strategies and approval of new drugs for the treatment of SLE, such as belimumab, a monoclonal anti-BLyS antibody, which has already been used in clinical practice in some Polish centers.

**New treatment strategy** Treatment of SLE continuously evolves. Currently, we follow the guidelines of the European League Against Rheumatism (EULAR) from 2008[6] and those of the American College of Rheumatology (ACR) from 2012[7] concerning LN. Nevertheless, they do not resolve all issues relating to SLE treatment. The main directions for a new strategy include the analysis of benefits of treatment with chloroquine (CQ) or hydroxychloroquine (HCQ), reduced use of GCs in favor of other more beneficial immunosuppressive therapies, and reduced use of high-dose cyclophosphamide (CTX). The launch of belimumab in 2011, the first biological agent in SLE treatment, has begun a new era in the therapy of SLE.[8,9] This new turn in the approach to an SLE patient is known as organ-specific therapy. The clinical course of the disease can be manifested by renal, skin, muscle, and joint symptoms, or it may have a form of severe hematological disorders or treatment-resistant neurological symptoms in the case of neuropsychiatric SLE. Therefore, organ-specific treatment is justified because serious symptoms, for example, from the kidneys or the nervous system, should be managed by intensification of therapy.

The level of disease activity is important when deciding on the therapy or its intensification. Until recently, there have been no objective measures to assess SLE activity. Now, there are activity and severity scores such as: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group (BILAG), or Systemic Lupus International Collaboration Clinics/American College of Rheumatology Damage Index (SLICC).[10] However, these tools are quite complex and their use in daily clinical practice is limited. Nonetheless, the knowledge of these tools facilitates a more objective assessment of the disease activity and correct therapeutic decisions.

**Hydroxychloroquine/chloroquine** Antimalarial agents, one of the oldest in rheumatology, are considered as a background therapy in patients with SLE. They are known to have multidirectional beneficial effects and to reduce mortality.[11] So far, they have been used in combination with GCs for mild disease with skin and joint involvement.[2] However, they are currently applied in all patients in combination with any new drug modifying the course of SLE. Antimalarials have an immunomodulatory effect by increasing lysosomal pH, inhibiting Toll-like receptors 9, 7, and 8, and inhibiting the synthesis of interferon-α. They also reduce mortality[12-14] and the number of flare-ups[15] as well as limit damage to various organs.[16,17] Metabolic benefits of HCQ and CQ are presented in **TABLE 1**. They have an antiaggregatory effect, particularly in SLE associated with antiphospholipid syndrome,[11] and hypolipemic effect. Moreover, they increase bone mineral density, allow to reduce GC doses, and have antiatherosclerotic effects. CQ or HCQ is recommended throughout the disease course, including during remission and flare-up. Both drugs may be used during pregnancy and lactation.[11,18-23]

Rheumatologists and ophthalmologists have raised concerns about possible toxic effects of antimalarials, particularly on the retina. However, in 4 clinical studies including 647 patients treated with CQ for over 10 years, toxic effects on

**TABLE 1** Effectiveness of antimalarial drugs according to the available data

| Quality of evidence | Clinical efficacy | HCQ/CQ | Data |
|---|---|---|---|
| high | reduction of SLE activity (during pregnancy)[19,21,22] | HCQ/CQ | 4 randomized controlled trials[15,18,19]<br>4 prospective studies[20-22]<br>2 retrospective cohort studies<br>1 retrospective data of extended randomized controlled trial |
| | reduction in mortality | HCQ/CQ | 1 case-control trial[12]<br>1 prospective study[13]<br>1 case-control with propensity analysis[14] |
| | significant reduction in glucocorticoid use | HCQ/CQ | 2 randomized controlled trials[18,19]<br>1 prospective study[20] |
| moderate | increase in BMD | HCQ | 2 cross-sectional studies |
| | protecting against thrombosis | HCQ/CQ | 5 prospective studies<br>2 cross-sectional studies<br>1 retrospective study |
| | protecting against organ damage[16,17] | HCQ | 2 prospective studies |
| low | reduction of severe flares[15] | HCQ | 1 randomized controlled trial<br>1 retrospective data of extended randomized controlled trial |
| | beneficial effect on lipid serum levels | HCQ/CQ | 7 prospective cohort studies |
| | protecting against osteonecrosis | HCQ | 1 case-control study |
| very low | reduction in vitamin D levels | HCQ | 1 cross-sectional study |
| | reduction in atherosclerosis | HCQ/CQ | 8 cross-sectional prospective studies |

Abbreviations: BMD – bone mineral density, CQ – chloroquine, HCQ – hydroxychloroquine, SLE – systemic lupus erythematosus

**TABLE 2** Immunosuppressive and immunomodulatory therapy in systemic lupus erythematosus (modified and based on Merill)[25]

| Therapy | Mild lupus | Moderate and severe lupus | LN induction remission | LN maintenance therapy | Refractory lupus |
|---|---|---|---|---|---|
| HCQ/CQ | + | + | + | + | + |
| AZA | | + | | + | + |
| MTX | | + | | | + |
| CsA | | | | | + |
| MMF | | + | + | + | + |
| CTX | | | + | | + |

Abbreviations: AZA – azathioprine, CsA – cyclosporine A, CTX – cyclophosphamide, LN – lupus nephritis, MMF – mycophenolate mofetil, MTX – methotrexate, others – see **TABLE 1**

the retina were observed only in 2.5% of the cases. In 6 other clinical studies including 2043 patients treated with HCQ over a similar period of time, the side effects were observed in 0.1% of the patients.[11] Currently, a safe cumulative dose is 460 g for CQ and 1000 g for HCQ. A standard ophthalmic examination at baseline and every 5 years during follow-up is recommended only for patients with risk factors for eye complications.[24]

**Immunosuppressive drugs** In patients with moderate and severe multiple organ involvement, the treatment of choice is immunosuppressive therapy. Its effectiveness may be enhanced by the early start of the treatment, achievement of the maximum effective dose tolerated by the patient, proper management, and, in particular, low incidence of possible side effects. If no clinical effects are observed, it is important to react quickly and change the drug or include biological agents (**TABLE 2**).[25]

Azathioprine (AZA), used since 1960s, methotrexate (MTX), or cyclosporine A (CsA) have been well known and used for many years. MMF, used by rheumatologists for a relatively short time, seems to be a good choice for the treatment of renal and extrarenal symptoms. Caution is recommended in the use of AZA and any increase in its doses should be well controlled because of possible hematological and hepatic complications.[26,27] Wider application of AZA may be hindered by genetically predisposed deficiency of the enzyme metabolizing AZA or a genetic polymorphism of other components of this pathway. MTX is used if arthritis symptoms predominate; however, according to experts, its doses should not exceed 15 to 20 mg/wk. In the United States, MTX is rarely used for this indication. For many years, CsA has been used in the treatment of LN. Currently, in individual cases, it may be an alternative to other drugs in recurrent,

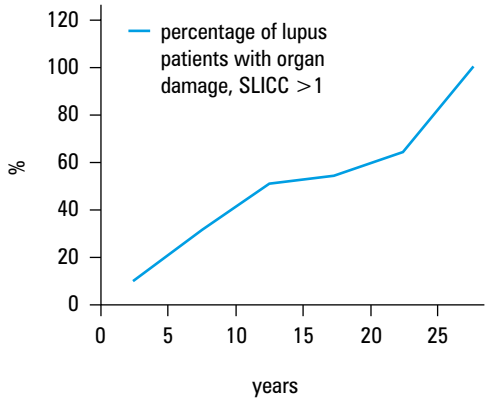


**FIGURE 1** Degree of organ damage in systemic lupus erythematosus assessed according to the Systemic Lupus International Collaboration Clinics / American College of Rheumatology Damage Index (SLICC) on the basis of the British data[2]

treatment-resistant SLE but its use is not generally recommended.

Serious multiple-organ symptoms often require more aggressive immunosuppressive therapy with CTX. The remission-inducing treatment should be intense, but relatively short, to minimize side effects. Currently, much smaller CTX doses are tried, reducing the infection risk and the possible toxic effect. An effective and preferred treatment regime inducing remission in LN is intravenous administration of CTX every 2 weeks (6 pulses of 500 mg at a total dose of 3 g).[28] Although there are no randomized studies, the above regime is successfully applied in the therapy of other multiple-organ symptoms. Some centers still prefer treatment with CTX pulses at 1000 mg dose per 1 infusion every month.

MMF is an alternative to CTX, which acts on T and B cells by inhibiting synthesis of purine nucleotides and thus blocking their proliferation. It is an oral immunomodulatory agent of high potency comparable to CTX. The advantages of CTX include intravenous administration, better compliance, and relatively low costs. MMF is a safe and well-tolerated drug, which is associated with lower infection rates, lower toxicity, and greater effectiveness than those of CTX in non-Caucasian patients. MMF is also much safer in patients planning pregnancy. A target MMF dose in Caucasian patients is 3 g/d, and treatment benefits can be expected after 8 weeks.

**Treatment of lupus nephritis** In 2012, the ACR published recommendations for the management of patients with SLE and kidney involvement.[29] The recommended treatment strategies are based on classification of active nephritis. According to the current guidelines, classes II to V of LN require immunosuppressive treatment (class I lesions are too mild and class VI too severe to require this treatment). The strongest recommendation concerns oral or intravenous GC-pulse therapy, and CTX or MMF used to induce remission in proliferative nephritis.[29] In LN, a response to first-line immunosuppressive therapy is achieved in 80% of the patients. Recurrence is observed in 35% of the patients, and in 10% of these patients, it leads to end-stage renal disease. Thus, after remission, maintenance therapy is introduced to prevent recurrence. In LN, the longest time to treatment failure is achieved by using CTX to induce remission and then by maintaining it with MMF. This regime proved more effective than AZA.[30] If severe lupus nephropathy recurs, remission-inducing treatment with CTX is recommended, and if it proves unsuccessful, then use of off-label rituximab (RTX) is advised. Most experts recommend to maintain immunosuppressive treatment in SLE patients with kidney involvement for 5 years, or even longer. An important component of treatment in LN patients is an adjunctive therapy that reduces additional factors affecting the kidneys and is highly recommended in all patients.[29] Apart from continuous use of HCQ/CQ (level C), in case of proteinuria of ≥0.5 g/d (level A) or hypertension (target blood pressure, ≤130/80 mmHg), angiotensin-converting-enzyme inhibitor or its receptor antagonists should be used. Statins should be included if low-density lipoprotein levels exceed 100 mg/dl (level C). If antiphospholipid antibodies are detected or nephrotic syndrome is diagnosed, use of acetylsalicylic acid should be considered as a standard anticoagulant treatment. In pregnant SLE patients with symptoms of internal organ involvement, use of AZA at a daily dose of up to 2 mg/kg is acceptable.

Despite the wide use of immunosuppressive drugs and their relatively good availability, their treatment potential does not seem to be maximized.[30] On the other hand, clinical studies still show their limited effectiveness.

Nevertheless, there is still no standard approach to SLE treatment. Thus, to improve long-term treatment results, the therapeutic procedure must be highly individualized and numerous factors should be considered: age, advancement of lesions, tolerance to various treatment method, and patient's compliance.

**Glucocorticoid therapy** A modern approach to GC treatment in SLE is to use these agents only in exacerbation and avoid them in a long-term therapy because of the increasing rate of organ damage. An effective immunosuppressive treatment (CTX, MMF, AZT) should induce low disease activity or remission and allow to reduce or even discontinue the use of GCs. However, most patients require a long-term use of GCs although it is associated with an increasing rate of organ lesions. After 15 years of standard long-term GC therapy, organ damage is observed in almost 50% of the patients (FIGURE 1).[2]

Complications in the musculoskeletal system are observed in 25% of the patients and in the central nervous system in 15% of the patients. They often conceal the clinical picture of the disease itself leading to an unjustified increase in the GC doses, which causes further damage. The extent of organ damage depends on dosage. Low prednisone doses of up to 6 mg/d are associated with low probability of organ damage but it significantly increases with higher doses

**TABLE 3** Prednisone exposure dose in patients with systemic lupus erythematosus and induced chronic organ damage vs. patients not receiving glucocorticoids

| Prednisone dose, mg/d | Hazard ratio |
|---|---|
| 0–6 | 1.16 |
| 6–12 | 1.50 |
| 12–18 | 1.64 |
| >18 | 2.51 |

(TABLE 3).[31,32] Of note, these complications result from a cumulative dose, to which a patient has been exposed during long-term treatment. Ischemic heart disease, bone fractures, or cataract result from a cumulative dose of GCs administered orally for a long time. On the other hand, hypertension, diabetes, thrombotic complications, or avascular necrosis are side effects of high-dose therapy. The use of GCs also increases the risk of complications related to traditional risk factors of cardiovascular diseases. One-third of SLE patients show mitral valve defect on echocardiography, which is a particularly unfavorable outcome of long-term therapy with GCs and requires much more attention from a clinician.[33] Long-term treatment with prednisone, even at low doses, significantly increases the risk of ischemic heart disease. An increasing body of reliable evidence forces rheumatologists to change the traditional approach to long-term treatment with SLE and be more reasonable and careful in the administration of GCs.

Another argument for not using GCs for long-term treatment is its significant effect on the risk of infection, particularly in the first 4 weeks of treatment and with the increasing dose.[34] Despite the general opinion of rheumatologists, immunosuppressive therapy dose not predispose to infectious complications to the similar extent as GCs. Thus, safe immunosuppression controlling SLE activity enables to minimize or discontinue GC doses.

Long-term administration of GCs offers a sense of comfort to patients, thus increasing their quality of life. However, patients usually recognize the benefits of GCs but are completely unaware of possible late complications. Full satisfaction and effectiveness of SLE treatment cannot be achieved until risk of complications and organ damage is not fully eliminated. By maximizing the potential of immunosuppressive therapy and combining it with new treatment possibilities offered by monoclonal antibodies, a more optimal, effective, and safer treatment can be achieved.

**Modern therapies for systemic lupus erythematosus** Growing knowledge about immune response and apoptosis abnormalities in the pathogenesis of SLE allows to identify target cells and protein molecules that could be used in the background treatment. This area of immunology forms the basis of a so called "treat-to-target" strategy that could certainly include SLE immunotherapy. Better availability and lower cost of modern technologies facilitate production of new biopharmaceuticals (usually monoclonal antibodies, which target the disease significantly more precisely than other traditional therapies).

Defects in cellular transmission between B and T cells, resulting in B-cell overreaction and overproduction of autoantibodies, are thought to be the cause of underlying disorders in SLE. Thus, identifying biomarkers for specific individual defects in cellular transmission pathways may be crucial for developing future target therapies in SLE (FIGURE 2).[35]

Modern therapies modulating the course of SLE include antiproliferative therapy inhibiting

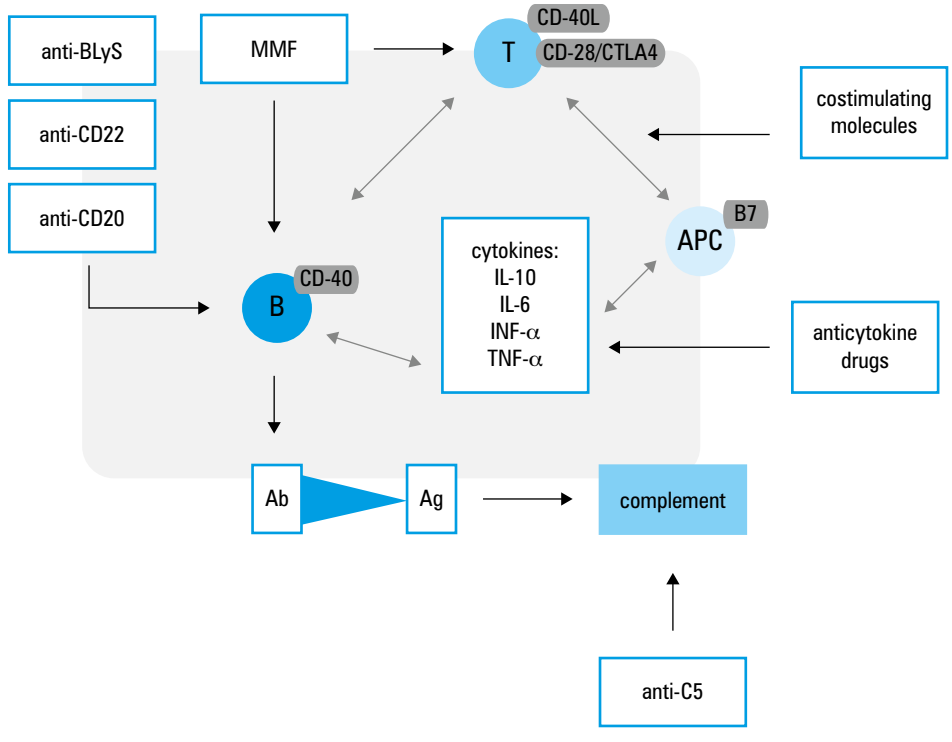


**FIGURE 2** Lupus immunotherapy
Abbreviations: Ab – antibody, Ag – antigen, anti-BLyS – anti-B--lymphocyte stimulator, anti-C5 – antibody against complement component 5, anti-CD20 – anti-CD20 antibody, anti-CD22 – anti-CD22 antibody, APC – antigen-presenting cell, B – B lymphocytes, CD28 – cluster of differentiation 28, CD40 – costimulatory protein, CD40L – CD40 ligand, CTLA4 – cytotoxic T-lymphocyte antigen 4, IL-10 – interleukin 10, IL-6 – interleukin 6, INF-α – interferon-α, T – T lymphocytes, TNF-α – tumor necrosis factor-α, others – see TABLE 2

**TABLE 4** Novel immunotherapy in patients with systemic lupus erythematosus

| Novel immunosuppressive or immunomodulatory therapy for SLE | |
|---|---|
| antiproliferative immunosuppression (T and B lymphocytes) | MMF |
| therapy targeted on B lymphocytes | anti-CD20 (rituximab, ocrelizumab)<br>anti-CD22 (epratuzumab)<br>anti-BLyS (belimumab)<br>anti-TACI-Ig (atacicept)<br>anti-IL-10 |
| inhibitors of costimulating molecules | CTLA4-Ig (abatacept)<br>anti-CD40 ligand |
| anticytokine therapy | anti-TNF-α<br>anti-IL-10<br>anti-IL-6R (tocilizumab)<br>anti-INF-α (rontalizumab, sifalimumab)<br>anti-TWEAK |
| complement inhibition therapy | anti-C5b-9 |
| nonspecific immunotherapy | intravenous immunoglobulins<br>peripheral blood stem cell transplantation |

Abbreviations: see TABLES 1 and 2 and FIGURE 2

B and T cells, blockers of costimulating molecules, anticytokine therapies, anticomplement antibodies, and other nonspecific methods of immunotherapy, such as intravenous administration of immunoglobulins or even bone marrow transplantation (TABLE 4).

Access to most of these methods is significantly limited. Belimumab has been approved and widely accepted but it is still unavailable as a reimbursed drug in Poland. A significant majority of these methods are currently being tested in clinical trials (e.g., epratuzumab).[36]

SLE is characterized by overproduction of antibodies by B cells; therefore, the development of therapies targeting B cells is crucial. Monoclonal antibodies may cause a total or partial B-cell depletion or inhibit factors supporting their survival.[37] The first biological drug approved for SLE treatment is belimumab, an antibody blocking the activity of soluble B-lymphocyte stimulator protein (BLyS). BLyS is involved in maturation, differentiation, and survival of B cells. It is a cytokine belonging to a tumor necrosis factor (TNF) ligand superfamily that plays a role of an important B-cell growth factor. Studies have shown that in patients with SLE, BLyS levels are increased, and in 20% to 30% of the patients they correlate with the levels of SLE-specific anti-dsDNA antibodies. Increased BLyS levels are a predictor of exacerbations and marker of disease activity.[38,39]

Belimumab is a human IgG1 monoclonal antibody specifically inhibiting BLyS molecules. It has been approved for treatment of SLE with high immunological activity. It is used at a dose of 10 mg/kg body weight intravenously once a month and is well-tolerated with no significant side effects. In a clinical study, it was used together with standard immunosuppressive therapy and GC. Half of the patients received immunosuppressants, 70% received HCQ/CQ, and 30% to 40% prednisone at a daily dose exceeding 7.5 mg. Patients who were additionally treated with belimumab showed significant clinical and immunological improvement and reduced disease activity according to the SLE Responder Index.[9,40,41] Biological therapy is most beneficial in patients with predominating joint, muscle, skin, and hematological symptoms and immunological activity (increased anti-dsDNA antibody levels and reduced levels of C3 and/or C4 complement component).[41] Moreover, in a group of LN patients, a better response to treatment was observed for proteinuria at a level of 0.5 to 2.0 g/d (20%) than for that at a level exceeding 2.0 g/d (6%). Unfortunately, clinical studies have shown that the full effect of belimumab was achieved only after 52 weeks of therapy. However, data from daily clinical practice is more optimistic and more promising than the results of the clinical studies.

Rituximab (RTX) is a biological drug known for its effectiveness in the treatment of rheumatoid arthritis and can be used for SLE. It is a monoclonal anti-CD20 antibody causing long-term B-cell depletion. Expectations concerning use of RTX for SLE were high before a clinical study phase was started, because of positive practical experience. However, the available data do not confirm the effectiveness of rituximab in this group of patients. Randomized controlled trials in patients with extrarenal SLE (EXPLORER trial) and with class III or IV LN (LUNAR and BELONG, respectively) were unsuccessful.[5,42] Nevertheless, RTX is still a necessary off-label option in patients with recurring LN, neuropsychiatric SLE, severe thrombocytopenia, leucopenia, and catastrophic antiphospholipid syndrome.[43-45] Clinical studies were also conducted in rheumatoid arthritis and SLE with the humanized anti-CD22 antibody, ocrelizumab; however, they were discontinued because of low effectiveness and possible side effects.

Another highly anticipated drug in SLE is abatacept. However, the results of randomized clinical trials are not promising. In SLE, signal transmission between the B cell, antigen-presenting cell (APC), and T cell is disrupted. Abatacept is a recombined human fusion protein of CTLA4 (cytotoxic T-lymphocyte-associated antigen-4) costimulatory molecule and immunoglobulin G. In physiological conditions, CTLA4 binds to CD80 and CD86 on APC cells and thus supports full activation of T cells. Despite the failure of clinical studies, numerous clinical case reports continue to give hope for the beneficial effect of abatacept in selected cases.[4]

The CD22 antigen located on B cells and responsible for the control of B-cell function is another new target for monoclonal antibodies. Epratuzumab is a humanized recombined IgG1 antibody binding CD22 without an immunomodulating effect.[46] It inhibits the proliferation of autoreactive B cells without complete depletion of these cells. It is still tested in clinical trials. Currently, it is

in phase III and shows positive clinical and laboratory effects as well as a good safety profile.[47]

In SLE, apart from the increased BLyS/BAFF/APRIL molecule levels, distribution of other cytokines such as interleukin (IL)-6, IL-21, or interferon-α (INF-α) is also disrupted. The increased IL-6 level is correlated with the activity evaluated by the SLEDAI and with anemia. Therefore, tocilizumab, an antibody binding the IL-6 receptor, approved for treatment of rheumatoid arthritis, can be an alternative for the treatment of SLE resistant to standard therapy.[48]

The level of INF-α is significantly increased in SLE patients. The IFN-α-neutralizing effect is currently being investigated in clinical studies: rontalizumab is a humanized anti-IFN-α antibody and sifalimumab is a fully human antibody. A significant arthritis component characteristic for SLE justifies the use of anti-TNF-α. However, considering the risk of infection caused by SLE itself as well as combined immunosuppressive therapy and biologics, this treatment is not applied. At the same time, its effectiveness is not fully satisfying.[49] There are numerous potential molecules and cytokines that can become targets in SLE treatment, such as Toll-like receptors, interferon-γ, inducible T-cell costimulator, tumor necrosis factor-like WEAK inducer of apoptosis, spleen tyrosine kinase, antigen CD40 ligand, Janus kinase, or IL-21. However, it is difficult to find a relationship between the results of clinical studies and daily clinical practice, and this is even more challenging for a heterogeneous chronic disease of unclear etiology.

Because both standard and nonstandard SLE therapies prove to be ineffective, we often apply methods justified by our practice and own experience, for example, intravenous administration of immunoglobulins.[50] Their mechanism of action is explained by several hypotheses including Fc receptor blockade in the phagocytic cells, cytokine production inhibition, effect on B cells crucial for SLE by inhibiting production of antibodies or reduction of T-cell proliferation. However, the actual mechanism underlying their effect has not been fully elucidated. So far, only 1 randomized clinical study on immunoglobulins in LN was published but showed no benefits of their use. However, it is difficult, if not impossible, to demonstrate the superiority and benefits of immunoglobulins when all other possibilities have been exhausted and often applied simultaneously.

The variety of immune disorders in systemic connective tissue diseases often leads to a decision of using autologous peripheral blood stem cell transplantation. Before applying this method, a careful clinical selection of patients should be conducted by weighing possible risks and benefits. Currently, it is thought that this procedure may be effective in patients resistant to standard therapies.

**Conclusion** The current treatment of SLE focuses on the objective assessment of disease activity, rationalization of therapy, and minimizing its toxicity. Defining targets for treatment, i.e., the "treat-to-target" strategy, has become the basis for the assessment of its effectiveness. Unfortunately, with standard treatment, only 3.4% of the patients achieve remission considered as no need to use GCs or immunosuppressants.[29]

However, the question remains of defining a possible therapeutic success in modern treatment strategy. New drugs, particularly, immunotherapy with monoclonal antibodies, allow to achieve different treatment objectives including reduction of mortality rate, clinical and immunological improvement, prevention of exacerbations, improvement in the quality of life, reduced demand for GCs (or even discontinuation), and reduction in the extent of irreversible damage. The near future will answer the fundamental question of whether therapeutic success in lupus treatment will be confirmed in randomized clinical trials.

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ARTYKUŁ POGLĄDOWY

# Nowa strategia leczenia tocznia układowego z uwzględnieniem leków biologicznych

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**SŁOWA KLUCZOWE**

immunosupresja, leki antymalaryczne, nowa strategia leczenia, terapia biologiczna, toczeń rumieniowaty układowy

**STRESZCZENIE**

Toczeń rumieniowaty układowy (*systemic lupus erythematosus* – SLE) jest heterogenną jednostką chorobową, w której aktywacja limfocytów B i przewlekły proces zapalny odgrywają główną rolę. Zarówno sama choroba jak i jej leczenie doprowadza do uszkodzeń wielu narządów i układów. Dotychczas pomimo intensywnego leczenia remisję choroby osiągało niewielu pacjentów, a odsetek powikłań narządowych istotnie wzrastał. Było to efektem stosowania przewlekłej kortykosteroidoterapii, przy stosunkowo niskim wykorzystaniu leków immunosupresyjnych. Dzięki nowej strategii leczenia oraz nowoczesnym możliwościom immunoterapii, możliwe jest obniżenie śmiertelności, ograniczenie wielonarządowych uszkodzeń, a tym samym znacząca poprawa jakości życia i rokowania chorych z SLE. Strategia leczenia *treat-to-target* pozwala na celowane leczenie, którego efektem ma być długotrwała remisja objawów. Opiera się ona na intensywnym leczeniu immunosupresyjnym przy jednoczesnej redukcji dawek sterydów i ograniczenia ich stosowania tylko do zaostrzeń choroby. Ideą leczenia jest również świadome wykorzystanie korzystnego potencjału leczenia podstawowego SLE jakim są leki antymalaryczne oraz standardowa terapia immunosupresyjna. Wraz z zarejestrowaniem do leczenia tocznia SLE pierwszego leku biologicznego, nastała nowa era. Nowoczesne terapie, a zwłaszcza leki biologiczne niosą ze sobą nowe perspektywy i możliwości indukcji remisji klinicznej i immunologicznej SLE.

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