Perspectives of Systemic Lupus Erythematosus Therapy
Perspektywy terapii tocznia układowego

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Abstract
Although systemic lupus erythematosus (SLE) is a complex autoimmune disease of unknown origin, recent advances in our understanding of its pathogenesis have suggested new, targeted approaches to therapy. In this review the underlying scientific rationale and results of clinical studies of new treatment approaches to SLE are discussed with a focus on cell-depleting therapies and cytokine blockade. It has become clear that B lymphocytes play a key role in the disease’s pathogenesis and aberrant interaction between B and T cells are critical to its emergence and progression. New agents that directly target immune cells which are abnormal in SLE include B-cell-depleting (anti-CD20) and -modulating (anti-CD22) antibodies. Another promising approach is to block co-stimulatory interactions between T and B cell (CTLA-4Ig). Immune cells can also be manipulated indirectly through cytokine effects (anti-BAFF). Pro-inflammatory cytokines can be blocked in SLE (anti-TNF, anti-IL-10). Most of the available data on these new treatment approaches stem from open-label trials, but controlled trials are underway (Adv Clin Exp Med 2008, 17, 4, 433–439).

Key words: SLE, treatment, monoclonal antibodies, rituximab.

Streszczenie

Słowa kluczowe: toczień układowy, leczenie, przeciwicel monoklonalne, rytuksymab.

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease with heterogeneity in clinical symptoms and disease course. It is characterized by multi-systemic organ involvement and gross immunological abnormalities, with significant tissue damage and organ dysfunction as a result of autoantibody formation and immune complex deposition [1]. The condition affects multiple systems and may present with a constellation of symptoms and signs, including arthritis, skin rashes, mucosal ulceration, weight loss, hematological abnormalities, and severe fatigue. The heart and lung may become involved and renal damage often leads to premature death if transplantation is not possible. Involvement of the central nervous system is less common but can lead to temporary or permanent disability or death. The earlier diagnosis in SLE, expanded therapeutic
options, and improved management of the disease have all contributed to improved prognosis for patients, with 5- and 10-year survival rates as high as 93 and 85%, respectively [2, 3].

The pathogenesis of SLE involves the interplay of genetic, environmental factors and the adaptive and innate immune systems. Abnormalities in the function, regulation, and interactions of immune cells, with T and B lymphocytes taking a central position, result in immune-complex-mediated deposition and inflammatory organ damage [4]. Typically, the disease follows a relapsing-remitting course with intermittent periods of disease activity (flare) interspersed with periods of relative quiescence. The frequency of flares tends to decline with increasing age and disease duration. It is uncertain whether this is due to an alteration in disease pathogenesis, age-related immune senescence, or the long-term effects of therapeutic immunosuppression. The prevalence of SLE ranges from 12.5 to 50 per 100,000 persons and appears to be increasing. This may be a result of increased recognition of the disease and/or increased survival following improvements in therapy.

Despite advances in disease management, options for the treatment of SLE remain limited. No new medications have been approved by regulatory authorities for the treatment of lupus in the past 40 years. Corticosteroids remain a common treatment for acute flares and are still often needed for the control of disease activity. Symptomatic treatments include non-steroidal anti-inflammatory drugs (NSAIDs) and antimalarials. For more aggressive but moderate disease, immunosuppressive agents are prescribed, such as azathioprine (AZA), methotrexate (MTX), leflunomide, and mycophenolate mofetil (MMF) used alone, with corticosteroids, or in combination, to suppress inflammation and to prevent flares. For more serious flares of disease, high-dose corticosteroids, intravenous immunoglobulin, cyclophosphamide (CYC), and/or high-dose mycophenolate or azathioprine may be used alone or in combination. All of these agents are associated with significant toxicity and/or difficulties in administration, while treatment failure remains common. Therefore there is an urgent need for new, effective, and well-tolerated treatments for patients with SLE. This article reviews published information regarding strategies that target cytokine pathways and/or immune cells critical to disease pathogenesis (Table 1).

### Role of B Cells in Human SLE

The pathogenic mechanisms of B cells in human SLE is difficult to elucidate. It is postulated that autoantibodies have a direct pathogenic role in the disease process, as exemplified by anti-double-stranded DNA (anti-dsDNA) in glomerular kidney disease and autoantibody-mediated cytopenias. B cells are abnormal in lupus, with an increased number of spontaneous immunoglobulin-secreting peripheral B cells, increased calcium flux on signaling through the B-cell receptor, and expression of high levels of costimulatory molecules such as CD80 and CD40 ligand on B cells. In addition to producing autoantibodies, B cells can take up and present autoantigens through specific cell-sur-

### Table 1. Biological agents in SLE therapy

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<tr>
<th>Immune target (Cel immunologiczny)</th>
<th>Agents (Substancja)</th>
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<tr>
<td>B-cell depleting (Neutralizowanie komórek B)</td>
<td>anti-CD20 – rituximab</td>
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<td>anti-CD22 – epratuzumab</td>
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<td>anti-CD52 – alemtuzumab</td>
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<td>Anti-cytokine (Substancje antycytokinowe)</td>
<td>anti-TNF – infliximab</td>
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<td>anti-BLyS – Lymphostat-B, TACI-Ig, BAFFR-Ig</td>
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<td>anti-IL-6 – MRA</td>
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<td>anti-INF</td>
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<td>Co-stimulation blockade (Blokowanie kostymulacji)</td>
<td>inhibition of connection CD28 and B7 – abatacept</td>
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<td>anti-CD154 – ruplizumab</td>
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<td>anti-CD137</td>
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<td>anti-CD19/21</td>
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<td>Inhibition of complement (Hamowanie składowych układu dopelniacza)</td>
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face immunoglobulins to T cells and help regulate and organize inflammatory response via cytokine secretion or regulation of other immune cells [5, 6]. The importance of these latter functions has been demonstrated in murine lupus, where B cells have been found to initiate the disease even when they are unable to secrete autoantibodies [7].

Recent data suggest a role in human lupus for high serum levels of B-cell stimulator (BlyS or BAFF), which is a factor of the tumor necrosis family. This cytokine promotes B-cell maturation, survival, and plasma cell differentiation and is increased in 20–40% of lupus sera [8, 9]. The current experience with therapies that target the B-cell compartment includes monoclonal antibodies to B-cell surface antigens, blocking of costimulatory molecules, and inhibition of cytokines with direct B-cell effects.

**Anti-CD20**

The pivotal role of B cells in the pathogenesis of SLE via both antibody-dependent and antibody-independent mechanisms suggests that B-cell depletion is a rational therapeutic strategy for the treatment of SLE. CD20 antigen is expressed on B cells throughout many stages of development, but not in plasma cells or stem cells, and provides a stable target for monoclonal antibodies targeting B cells.

The development of rituximab has raised the hope of a new therapeutic approach for autoimmune diseases such as rheumatoid arthritis (RA) and SLE that are at least in part B-cell mediated. Rituximab is a chimeric mouse and human monoclonal antibody against the B cell-specific antigen CD20, which efficiently depletes B lymphocytes in vivo [10]. It was first approved by the FDA for the treatment of refractory non-Hodgkin’s B-cell lymphomas in 1997 [11]. Rituximab is generally well tolerated, with only minor effects on immunoglobulin levels and no increase in the frequency of infections. Rituximab has the advantage of being less immunosuppressive because CD20 expression is restricted to B cells, so the effects of anti-CD20 should be directly on the B-cell compartment, with relative sparing of T cells and plasma cells. There are positive data on the use of rituximab in a variety of autoimmune diseases, including IgM-antibody-associated polyneuropathy, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia [12], dermatomyositis [13], and Wegener’s granulomatosis [14]. Although these were open studies, a double-blind placebo-controlled trial demonstrating the effectiveness and safety of rituximab in RA has been reported [15].

A number of open studies and some phase III randomized controlled trials of rituximab in the treatment of SLE have now been reported [12, 16–21]. The clinical outcome was assessed by standard disease activity measures (SLEDAI: Systemic Lupus Erythematosus Disease Activity Index, SLAM: Systemic Lupus Activity Measure, and the BILAG: British Isles Lupus Assessment Group). Rituximab administration was associated with a clinically meaningful decrease in global lupus disease activity in 80% of patients, with reported follow-up periods ranging from 3 to 46 months. In patients with lupus nephritis treated with rituximab, reduction in proteinuria, stabilization or improvement in renal function, and resolution of nephritis urine sediment have been observed as well as improvement in disease activity assessed by repeat biopsy. In central nervous system lupus, resolution of symptoms has also been reported. All these trials determine the safety, efficacy, and dose response of rituximab added to current therapy (mainly steroids and immunosuppressive drugs) in the treatment of active SLE, lupus nephritis and CNS lupus. In the majority of patients with effective B-cell depletion, the clinical signs were significantly improved at 2 and 3 months and improvement persisted for 8–12 months. Based on these experiences, rituximab is safe and promising in the treatment of SLE, but a high dose of rituximab is necessary, possibly with the addition of other immunosuppressive agents to ensure consistent B-cell depletion, prevent the development of human anti-chimeric antibodies (HACAs), induce serologic response, and enhance clinical efficacy.

Rituximab is the best studied B-cell depletion therapy and was well tolerated in SLE when administered with premedication (steroids, antihistaminic and antipyretic drugs). It can be efficacious in refractory SLE cases with prolonged remission. High doses of rituximab are necessary for consistent B-cell depletion, and serologic responses are inconsistent, perhaps because of the presence of long-lived autoreactive plasma cells. Multicenter randomized controlled trials of rituximab therapies in SLE are needed to confirm the preliminary results of open studies and it will probably soon be approved for use in patients with SLE [22].

Open trials of full-dose rituximab as monotherapy in SLE with active visceral disease are being conducted and the initial results are very promising. The treated patients demonstrated clinical responses defined by improvement in SLEDAI, with short- and long-term remission. Even in the short-term responders, disease control was better post rituximab [23]. Additionally, fully humanized anti-CD20 monoclonal antibodies are under evaluation [24].
Anti-CD22 and Anti-CD52

An open-label pilot study of anti-CD22 (epratuzumab) in the treatment of active SLE patients was reported [25]. The drug was well tolerated, with the majority of patients experiencing a > 50% improvement on the BILAG scale. Alemtuzumab is another monoclonal antibody to anti-CD52 antigen. This antigen is present on B and T lymphocytes in active SLE patients [26].

Inhibition of Co-Stimulation

As an alternative to selective B-cell depletion, there has been interest in targeting co-stimulatory signaling pathways. CD40 binding to CD40 ligand is one of the most important signals to activate B cells. Direct inhibition of the CD40-CD40L pathway has been demonstrated to be effective in lupus mouse models [27]. In humans, anti-CD154 (ruplizumab) was used in a study focused on patients with lupus nephritis and showed improvement in serology and hematuria. Unfortunately, this study was stopped because of unexpected thromboembolic events [28].

Another co-stimulatory pathway includes the CD28 and CTLA4 receptors and their B-cell ligands B7. Blockade of B7 stimulation on B cells with a fusion protein (abatacept) has demonstrated promising results and safety in human clinical trials in RA patients [29], but it has yet to be used in human SLE [30], although clinical studies are in the planning stages.

Anti-Cytokine Therapies

The alternative to directly targeting immune cells is to interfere with their messengers, such as cytokines. Most investigated cytokines have been found to be dysregulated in SLE. BLyS (BAFF) is a cytokine of the TNF family that binds to membrane receptors expressed on B cells. It has profound effects on B-cell survival, stimulates plasma-cell differentiation, might have differential effects on autoreactive B cells, and correlates with SLE activity and levels of anti-dsDNA autoantibodies [31]. Lympho-Stat-B is a fully human monoclonal antibody that specifically binds to BAFF and has demonstrated safety and biological activity with significant reductions in peripheral B cells. Alternative approaches to inhibiting BAFF, including the use of BAFFR-Ig and TACI-Ig, are also under development [32].

Tumor Necrosis Factor (TNF) and Anti-TNF Therapy

TNF is a pleiotropic cytokine that exerts several functions in the immune system and can either promote or relieve autoimmunity. TNF blockade in patients with rheumatoid arthritis or Crohn’s disease (anti-TNF drugs are approved for these diseases) is associated with the development of ANA, anti-dsDNA, and anticardiolipin antibodies as well as with rare cases of drug-induced lupus-like syndromes, all of which disappeared after therapy was stopped [33]. TNF concentrations and soluble TNF receptors are increased in the sera of SLE patients and associated with disease activity. Moreover, TNF was found in the inflamed kidneys of patients with lupus glomerulonephritis and correlated with histological disease activity, and renal cells express TNF receptors [34]. These findings argue for a pathogenic role in the local inflammatory processes of SLE.

Infliximab (an anti-TNF-α monoclonal antibody) were administered to patients with moderate SLE with refractory lupus nephritis or lupus arthritis on an immunosuppressive medication of azathioprine or methotrexat and low-dose steroids. No infusion reactions occurred, but in the absence of azathioprine or methotrexate there were severe infusion reactions commonly found in others, suggesting that the combination with immunomodulators is essential [33]. Some patients experienced an increase in anti-dsDNA antibodies; however it proved to be transient and did not lead to lupus flare. The inflammatory organ disease improved rapidly in all patients; lupus arthritis remitted within days and significant long-lasting renal response was observed.

Similarly, other clinical observations found beneficial effects of TNF blockers with regard to lupus arthritis and refractory skin disease [35]. These clinical results suggest that TNF blockade, when combined with azathioprine or methotrexate, might be safe and effective in SLE patients, particularly those with lupus nephritis. It is imperative now to study TNF blockade in SLE in a double-blinded placebo-controlled fashion to evaluate the role of anti-TNF drugs in SLE therapy appropriately.

Anti-IL-10 Therapy

IL-10 is overproduced by the B cells and monocytes of patients with SLE, increased in sera, and associated with disease activity [36]. In the absence of human or humanized anti-IL-10 antibody, a murine monoclonal antibody was adminis-
tered to six SLE patients. All patients had skin and joint involvement and constitutional symptoms despite corticosteroid, chloroquine, azathioprine, or methotrexate therapy [37]. All patients developed antibodies against the murine protein. This therapy was well tolerated and rapid clinical improvement was seen in all six patients. Despite the end of therapy after three weeks, therapeutic benefits were stable during the next six months. Although this was a small, open-label study in patients with relatively mild disease, these findings suggest that anti-IL-10 therapy with an agent suitable for use in humans would probably benefit some patients with SLE.

**Anti-IL-1**

IL-1 can be increased by TNF and by autoantibodies to dsDNA. In a first open trial of anakinra (IL-1Ra) in four patients with SLE and severe lupus arthritis, anakinra improved arthritis in all patients and the therapy was safe [38]. The potential effect on lupus nephritis has not yet been investigated.

**Anti-IL-18**

IL-18 is a pro-inflammatory cytokine related closely to IL-1 which is activated by interleukin-1â-converting enzyme (ICE) and is increased in the sera of SLE patients [39]. So far, IL-18 blockade has not been reported in SLE patients, but agents suitable for this purpose are currently being tested in other rheumatic diseases.

**Anti-IL-6**

IL-6 is another pro-inflammatory cytokine secreted by macrophages and T cells and found to be increased in SLE sera [34]. It has been shown to activate B cells and drive plasma-cell differentiation. IL-6 is induced by anti-dsDNA antibodies and is also highly expressed in SLE glomerulonephritis. IL-6 blockade might also be beneficial in SLE patients.

**IFN-α**

Interferon-α (IFN-α) has been associated with B-cell lymphopenia, germinal center differentiation, and the generation of plasma cells, findings of obvious relevance to the peripheral B-cell subpopulation abnormalities characteristic of SLE. Although the precise role of IFN in the autoimmune process remains to be fully elucidated, the abundant evidence that IFN-α contributes to disease pathogenesis has made it an attractive therapeutic target [40]. This concept is supported by the development of a lupus-like illness in patients treated with IFN-α. Humanized antibodies are likely to be available in the near future.

In summary, new approaches that target immune cells and cytokine pathways in SLE show great promise. Several open clinical observations suggest that B-cell depletion with rituximab treatment can improve clinical manifestation of SLE, indicating that B cells are crucial not only for the development of SLE, but also for continued activity of established disease. Although much fewer patients were treated with anti-TNF agents, the experience with infliximab suggests a significant benefit in rapidly reducing inflammation and possible long-term effects on proteinuria and hematuria, despite the transient occurrence of autoantibodies. Several other cytokines, such as IL-6 and IL-18, might be targeted in the future. Combination therapy with different biological agents could potentially provide better efficacy by synergistically targeting different arms of the immune system. One more compelling argument for the continued development of biologics in SLE is the potential for inducing long-term remission and improvement in prognosis for patients suffering from systemic lupus erythematosus.

**References**


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