Target Therapy in Systemic Lupus Erythematosus: A Narrative Literature Review

Muhamad Delfin\textsuperscript{1*}, Raveinal\textsuperscript{2}, Dwitya Elvira\textsuperscript{2}

\textsuperscript{1}Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia
\textsuperscript{2}Division of Allergy and Immunology, Department of Internal Medicine, Faculty of Medicine, Universitas Andalas/Dr. M. Djamil General Hospital, Padang, Indonesia

**A B S T R A C T**

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by the presence of autoantibodies against cells and involves many organ systems in the body. The Lupus Foundation of America estimates that around 1.5 million cases occur in America and at least 5 million cases occur worldwide. Every year it is estimated that there are around 16 thousand new cases of SLE. Various pro- and anti-inflammatory cytokines such as transforming growth factor (TGF), interleukin-10, B cell activating factor (BAFF), interferon-\(\alpha\), interleukin-17, and interleukin-23 play an important pathogenic role. Disruption of apoptotic cells and immune complexes is an important contributor to the development of this disease. Loss of immune tolerance increases antigenic load, excessive role of T cells, impaired B cell suppression and impaired transition of the immune response from T helper 1 (Th1) to Th2 which causes hyperactivity of B cells and produces pathogenic autoantibodies. The management of cases of severe or refractory SLE to conventional therapy has attracted a lot of attention in recent years, so that many researchers have developed several targeted therapies that have been tested on SLE, such as anti-CD 20 and CD 22 antibodies and BAFF inhibitors found in B lymphocyte cells. The Rituximab anti-CD 20 antibody target has been clinically proven to be able to improve the severity of SLE, while the effectiveness of other targeted therapies is still under research.

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by the presence of autoantibodies against cells and involving many organ systems in the body.\textsuperscript{1} The Lupus Foundation of America estimates that around 1.5 million cases occur in America, and at least 5 million cases occur worldwide. Every year, it is estimated that around 16 thousand new cases of lupus occur. The prevalence of SLE in Asia, according to Tanaka et al. (2022), ranges from 3.7-127 per 100,000 people, with the highest prevalence in Hong Kong at 58.8 per 100,000 people.\textsuperscript{2,3}

The etiopathogenesis of SLE occurs due to the disruption of apoptotic cells and immune complexes, which are important contributors to the development of this disease. Loss of immune tolerance increases antigenic load, excessive role of T cells, impaired B cell suppression, and impaired switching of the immune response from T helper 1 (Th1) to Th2, which causes B cell hyperactivity and the production of pathogenic autoantibodies. Immune responses that are exposed to external/environmental factors such as ultraviolet radiation or viral infections over a long period of time can also cause dysregulation of the immune system.\textsuperscript{4}

According to Durcan et al. (2017), there are a number of targeted therapies that have been developed and tested in SLE. Meanwhile, according to Parodis et al. (2020), to inhibit the B cell response in SLE, there are two main pathways currently used, namely inhibition of B lymphocyte activating factor (BAFF) and depletion of B cells targeting cell surface receptors such as anti-CD20 and anti-CD22. Therefore, this
A report was created to discuss the latest therapies that can suppress the formation of autoantibodies, or what is known as targeted therapy.5,6

**Definition & epidemiology**

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of multiple autoantibodies against many cells, especially nucleic acids and nuclear proteins, involving many organ systems in the body.7,8 The Lupus Foundation of America (LFA) estimates that around 1.5 million cases occur in America and at least 5 million cases occur in the world. Every year it is estimated that around 16 thousand new cases of SLE occur. According to Barber et al (2021), the estimated number of SLE cases in North America ranges from 48-366.6 per 100,000 people, in Europe it varies between 29-210 per 100,000 people, in England it is 97 per 100,000 people and in Greece it is 123 per 100,000 people. Research conducted by Izmirl et al (2021) found that the prevalence of SLE in women was 9 times higher than men, namely 128.7:14.6 per 100,000 people. The incidence rate of SLE in Asia according to Tanaka et al (2022) ranges from 0.9-8.4 per 100,000 people per year with a prevalence ranging from 3.7-127 per 100,000 people. The prevalence of SLE in China is 10-70 per 100,000 people, Hong Kong is 58.8 per 100,000 people, Korea is 18.8-21.7 per 100,000 people and Japan is 3.7-37.7 per 100,000 people.9,10 According to Hamijoyo et al (2019), the prevalence of SLE in Indonesia is 0.5% of the total population with a tendency to increase in the number of incidents every year and women aged 15-44 years are more frequently affected. Polyclinic data in several hospitals in Indonesia shows an increase in visits by SLE patients, namely 17.9-27.2% (2015), 18.7-31.5% (2016) and 30.3-58% (2017).4,11

**Etiopathogenesis**

SLE is thought to involve complex and multifactorial interactions between genetic variations and environmental factors. Several cohort studies identified several new loci and genetic variants associated with SLE. Abnormalities in the phenotype and function of T and B lymphocytes, disturbances in cytokines and soluble mediators of the adaptive immune system are important factors in the pathogenesis of SLE. Innate immune cells also play a role in disease pathogenesis.1 The phagocytic cells in lupus reduce their capacity to eliminate immune complexes, this causes large amounts of autoantigens and autoantibodies with an increase in the number of activated B cells and plasma cells, and autoreactive T cells resulting in an increase in the number and function of Th1 and Th17, all of which increase the production of autoantibodies. and cause tissue damage. This damage begins with the deposition of autoantibodies and/or immune complexes followed by destruction mediated by complement activation and the release of cytokines or chemokines. The pathogenesis of SLE can be seen in Figure 1.1,12,14

---

**Figure 1. Pathogenesis of SLE.**12
Clinical manifestations

Skin involvement in SLE occurs in almost 90% of patients and includes specific manifestations of lupus such as acute cutaneous lupus, subacute cutaneous lupus, and chronic cutaneous lupus such as discoid lupus and lupus profundus. Kidney involvement occurs in approximately 50% of lupus patients, especially in certain ethnic groups, namely African-Americans (70%). Urine protein levels above 500 mg/24 hours are related to histopathological lupus nephritis and require immediate renal biopsy. In addition, clinical and serological activity of hypocomplementemia and elevated anti-dsDNA antibodies suggest lupus nephritis. Various neuropsychiatric manifestations are also associated with SLE including seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state.

Treatment

Drugs used in SLE include conservative drugs to reduce pain such as NSAIDs, antimalarial drugs, corticosteroids, and immunosuppressants. The decision to use medication in SLE refers to disease activity as assessed by the MEX-SLEDAI score. Biological therapy such as belimumab or rituximab may be considered if the patient does not respond well to immunosuppressant therapy. Intravenous immunoglobulin and plasma pheresis may be considered in patients with refractory cytopenias, thrombotic thrombocytopenic purpura (TTP), progressive neuropsychiatric SLE, and catastrophic antiphospholipid.

B cell maturation and differentiation

Humoral immunity refers to an adaptive immune defense mechanism mediated by antibodies secreted by B lymphocytes or B cells. B cells are produced from hematopoietic stem cells in the bone marrow. B cells are formed from Hematopoietic stem cells (HSC) in the bone marrow and follow the pathway of lymphoid and lymphoblast stem cells. The development and survival of B cells depends on stimulation by the B cell activating factor, namely tumor necrotizing factor (TNF), also called B lymphocyte activating factor (BAFF) or known as B lymphocyte stimulator (BLyS). BAFF is a member of the TNF ligand superfamily of proteins, and is produced by myeloid and stromal cells.

At the beginning of B cell maturation through assessing the function of their antigen binding receptors. This process occurs through positive selection for B cells with normal functional receptors. Negative selection mechanisms are then used to eliminate autoreactive B cells and minimize the risk of autoimmunity. Negative selection of autoreactive B cells undergoes an elimination process through apoptosis, and receptor modification so that they are no longer autoreactive. Immature B cells that pass selection in the bone marrow then travel to the spleen/spleen for the final stage of maturation. In the spleen, naive B cells are formed, namely mature B cells that have not been activated.

Figure 2. B Cell Differentiation.
Upon encountering an antigen, naïve B cells proliferate within the B cell follicles producing short-lived antigen-secreting cells in the germinal center (GC). B cells undergo proliferation and hypermutation within the GC to produce long-lived memory B cells, plasmablasts (PB) and plasma cells (PC) that are capable of secreting antibodies. Effector B cells can secrete antibodies at a rate of about 2000 molecules per second and secrete antibodies into the blood.\textsuperscript{16}

**Classification of B cells**

There are four main types of B cells, namely transitional B cells, naïve B cells, plasma B cells, and memory B cells, all of which have their own purposes in the B cell maturation process.\textsuperscript{17}

**Transitional B cells**

B cells in the immature bone marrow differentiate through transition stages into functionally competent follicular naïve B cells. Transitional B cells are the link between immature and mature B cells. This type of transitional B cell cannot fight against pathogens.\textsuperscript{17}

**Naive B cells**

Naive B cells are the next process after transitional B cells. Once B lymphocytes mature, either in the bone marrow or secondary lymphoid organs, naïve B cells remain naïve cells until they are activated. Activation occurs when mature B cells are exposed to antigens specific to their B cell receptors. Upon activation, naïve B cells can become plasma B cells or memory B cells.\textsuperscript{17}

**Plasma B cells**

Plasma B cells or also called effector B cells, are large cells with a very large endoplasmic reticulum (ER) that produce large amounts of antigen-specific antibodies such as immunoglobulin (Ig) IgM, IgD, IgG (types 1-4), IgA and IgE. Plasma cells respond to signaling chemicals released by T cells during infection and continue to make antibodies to fight the infection until it is controlled or eliminated.\textsuperscript{17}

**Memory B cells**

One important variant of B cells is memory B cells, a type of B cell that is needed to build long-term immunity in the body. These cells remain in the bloodstream after the infection has resolved. If the host is re-exposed to the same antigen a second time, memory B cells can quickly activate with the help of T cells.\textsuperscript{16,17}

**The role of B cells in SLE**

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organ systems. SLE disease is characterized by loss of immune tolerance which causes an immune response against endogenous cytoplasm. This autoantigen process produces clones of autoantibody plasma cells systemically.\textsuperscript{18} In SLE there is hyperactivity of B cells and increased expression of Toll-like Receptors (TLR) compared to healthy individuals, which can indicate an inflammatory response. B cells play an important role in several aspects of SLE pathogenesis. B cell depletion has been used successfully to treat autoimmune diseases such as SLE, rheumatoid arthritis and vasculitis. According to Parodis et al (2020) B cell targets in SLE have been developed and there has been a lot of related research, and have been developed as a treatment to assess clinical improvement. Monoclonal antibodies against B cells that activate BAFF cytokines, and the target is B cells in early maturation stages.\textsuperscript{6} According to Durcan et al (2017) there are a number of targeted therapies, which have been developed and tested in SLE. Parodis et al (2020) To inhibit the B cell response in SLE, there are two main pathways currently used, namely BAFF inhibition, and B cell depletion targeting the cell surface receptors CD20, CD22.\textsuperscript{19}
Targeted therapy in SLE

The treatment of cases of lupus nephritis that are refractory to conventional therapy has attracted quite a lot of attention in recent years. Clinicians are trying to overcome this, so the newest agent therapy is used, namely a biological agent aimed at suppressing the process of autoantibody formation in SLE conditions. Currently, targeted therapy is stated to have efficacy as a steroid-sparing agent and as an alternative therapy for refractory SLE/lupus nephritis. There are a number of targeted therapies that have been developed and trialled in SLE, namely B cell depletion targeting the cell surface receptors CD20, CD22 and BAFF inhibition.\(^{19}\)

Anti-CD-20 antibodies

B cells have several specific markers, namely CD20, CD22, CD19, B cell activating factor receptor (BAFF-R) which are proteins found on the surface of B cells which have their respective roles in B cell development.\(^{6}\)

Rituximab

Rituximab is a human monoclonal antibody against the B-cell-specific antigen CD20 which is expressed early in the development of B lymphocytes. Administration of Rituximab causes rapid depletion of B cell CD20 lymphocytes. According to Durcan et al (2017) Rituximab is a chimeric monoclonal antibody that specifically targets CD20 on B-cells which causes depletion of mature B-cells and B-cell precursors. Postal et al (2017) Rituximab has been used in refractory patients and improved in up to 89% of patients.\(^{6,19,20}\)

Rituximab is a monoclonal antibody that selectively attacks the B-cell CD-20 receptor. B-cells play an important role in cytokine production, presentation of self-antigens that activate T-cells, and are able to produce autoantibodies. CD20 is a phosphoprotein that is expressed on almost all B-cells. When rituximab binds to the CD-20 antigen on the surface of B-cell lymphocytes, it causes lysis of complement and antibody-dependent B-cells so that the number of B lymphocytes decreases. By reducing B-cells, rituximab can prevent the formation of auto-reactive cells that produce antibodies.\(^{21}\)
According to Samotji et al (2019), a long-term regimen of rituximab without oral corticosteroids shows efficacy in patients with Lupus nephritis. Two doses of rituximab (1 g/dose at 14 day intervals) and 2 doses of IV methylprednisolone (500 mg on days 1 and 15) were administered to the patient in combination with MMF therapy. Complete and partial responses at week 52 were obtained in 52% and 34% of participants, respectively. According to research by Lu et al (2009) Rituximab is effective in the treatment of SLE that fails to respond to conventional standard therapy. In this study, of 45 patients it was reported that 19 patients (42%) achieved complete remission, 21 patients (47%) achieved partial remission, 5 patients (11%) failed to achieve remission.

According to research by Weidenbusch et al (2013), Rituximab is effective in treating refractory lupus nephritis using a regimen of 375 mg divided into 4 doses and 1000 mg divided into 2 doses every week. In this study, it was reported that 87% of patients achieved total and partial remission in class III lupus nephritis, 76% in class IV lupus nephritis, and 67% in class V lupus nephritis.

Ocrelizumab
A new monoclonal anti-CD20 antibody has been developed, namely Ocrelizumab, which is a recombinant human monoclonal anti-CD20 antibody. Ocrelizumab was approved by the FDA in 2017 as a treatment for multiple sclerosis. However, the ocrelizumab trial in SLE patients is still in phase III. In the research of Mysler et al (2013). Patients with refractory lupus nephritis responded to therapy with ocrelizumab numerically but not statistically (P = 0.065) compared to placebo. From this study the response to therapy was 54.7% who received placebo, 66.7% who received ocrelizumab 400 mg, 67.1 % who received ocrelizumab 1000 mg.

Anti-CD-22 antibody (Epratuzumab)
Epratuzumab is a monoclonal antibody directed against the CD22 antigen and is well tolerated. Epratuzumab is a recombinant human IgG monoclonal antibody directed selectively against the CD22 antigen on the surface of mature B cells. CD22 is a B cell-specific surface antigen involved in the modulation of BCR signaling, cellular activation, and B cell survival. Epratuzumab acts as a nondepleting
immunomodulatory agent of B cell proliferation and decreases the expression of adhesion molecules and the synthesis of proinflammatory cytokines, such as interleukin-6 (IL-6) and TNF-α. Epratuzumab dose is 600 mg every week or 1,200 mg every week. This drug has been studied in phase II lupus nephritis clinical trials. The British IsSLE Lupus Assessment Group (BILAG)-based lupus assessment was the first to be used in a phase IIb clinical trial of epratuzumab.

According to research by Wallace et al (2016), administration of epratuzumab to SLE patients was well tolerated in 380 patients for 108 weeks, however the epratuzumab study is still in phase II clinical trials so an extension of time is needed to provide further results in the treatment of SLE.

B cell activating factor (BAFF) inhibitors

B cell activating factor (BAFF) or also known as B lymphocyte stimulator (BLyS) and A proliferation-inducing ligand (APRIL) is a member of the TNF ligand superfamily of proteins produced by myeloid and stromal cells. B cell development and survival depend on stimulation by BAFF. B cells have several specific markers, namely CD20, CD22, CD19, and B cell activating factor receptor (BAFF-R). These specific markers have their respective roles, such as BAFF-R, whose function is to increase the lifespan of B cells.

Belimumab

B lymphocyte stimulator protein (BLyS), also known as A proliferation-inducing ligand (APRIL) is a growth factor that is important for maintaining the survival and maturation of B cells. BLyS binds to three different B cell receptors, namely transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI), B cell maturation antigen (BCMA), and BAFF receptor. Samoti et al (2019) stated that the intravenous dose of belimumab given at a dose of 10 mg/kg body weight on days 0, 14, and 28 and then every 28 days has been approved by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and the National Institute for Health and Care Excellence (NICE). Belimumab is indicated for the treatment of adult patients with seropositive SLE with active skin or joint disease, who have not responded to standard treatment, excluding patients with lupus nephritis (LN) and severe central nervous system (CNS) involvement. Huang et al (2022) stated that Belimumab is effective in the treatment of SLE which provides a reduction in SLE activity based on the SLEDAI score (57%), a reduction in the incidence of flares (66%) and can reduce the use of prednisone by up to 43% of the initial dose. Wise et al (2020) stated that Belimumab has been proven to provide a therapeutic response in SLE patients, of 836 patients who received Belimumab 200 mg sc (10 mg/kg/bb) every week, an SLE Responder Index – 4 (SRI) was obtained with a result of 61.4 % (P = 0.0006). Carter et al (2013) stated that BAFF levels were significantly higher during a flare and higher compared to before targeted therapy, so that belimumab or B cell activating factor (BAFF) inhibitors can be given to SLE patients who have received targeted therapy.

Atacicept

According to Samoti et al (2019), Atacicept is a human recombinant fusion protein that neutralizes BAFF and APRIL. This agent is a soluble, membrane-associated inhibitor of BAFF. Atacicept at a dose of 150 mg SC 2x a week for 4 weeks, then once a week there was a severe decrease in serum IgG levels and serious infections. Then there is a dose adjustment with atacicept (75 mg or 150 mg 2x per week for 4 weeks, then 1x per week for 48 weeks). The analysis showed a relationship between the dose administered and a reduction in Ig concentration and frequency of exacerbations. Atacicept provides significant improvement in SLE Responder Index 4 (SRI), but is still in phase III trials.

2. Conclusion

Systemic lupus erythematosus is an autoimmune disease characterized by systemic inflammation associated with the deposition of autoantibodies and immune complexes which results in damage to various
organs. In severe and refractory SLE conditions, targeted therapy modalities can be considered. Rituximab Targeted Therapy has been clinically proven to improve the severity of SLE.

3. References


