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Review Article

New Therapy for Systemic Lupus Erythematosus: A Review Article

Nanda Rachmad Putra Gofur[1], Aisyah Rachmadani Putri Gofur[2], Soesilaningtyas[3], Rizki Nur Rachman Putra Gofur[4], Mega Kahdina[4] and Hernalia Martadila Putri[4]

[1]*Department of Health, Faculty of Vocational Studies, Universitas Airlangga, Indonesia*

[2]*Faculty of Dental Medicine, Universitas Airlangga, Indonesia*

[3]*Department of Dental Nursing, Indonesia*

[4]*Faculty Of Medicine, Universitas Airlangga, Indonesia*

***Corresponding author:** Nanda Rachmad Putra Gofur, Department of Health, Faculty of Vocational Studies, Universitas Airlangga, Surabaya, Indonesia

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Abstract

Introduction: SLE is a multisystem autoimmune disease that can exacerbate and remit. This disease attacks various organs such as the skin, kidneys, musculoskeletal, nervous, cardiovascular, and oral cavities. As many as 50-70% of SLE patients have kidney problems. Renal involvement is a major cause of high morbidity and mortality in this population. Clinically, renal disease in SLE begins with asymptomatic proteinuria which then progresses rapidly to progressive glomerulonephritis with renal failure. About 95% of SLE patients can show musculoskeletal manifestations. Arthralgia, joint deformities, temporomandibular joint abnormalities and avascular necrosis have been reported in SLE patients. Systemic lupus erythematosus (Systemic Lupus Erythematosus / SLE) cannot be cured, but there is a series of active phases (flares) and the calm phase of the disease. The goals of available treatment are to reduce the severity of symptoms, prevent organ damage, and minimize their impact on the life of people with SLE. The type of drug and dose given to one lupus sufferer is not the same as other lupus sufferers and can change from time to time depending on the symptoms you feel and the severity of them. Therapy in lupus is very individualistic depending on the severity of the disease, the goal is to suppress disease activity by weighing the risk of side effects. In life-threatening patients, therapy is carried out as aggressively as possible by administering very high doses of the drug and carried out in a hospital. New therapy is needed in lupus patients so that life expectancy increases, and complications can be avoided.

Discussion: In recent years, the treatment of LES nephritis has been based on several years of high doses of immunosuppressants and NSAIDs in mild cases. Immunosuppressants used can be metotrexan, corticosteroids, cyclophosphamide, cyclosporin A, azatiophrine and mycophenolate mofetil. This kind of approach is usually used in severe cases such as lupus nephritis by using several drug combinations. Another therapy for LES is by changing the lifestyle (lifestyle) by maintaining health with exercise, diet and vitamins and avoiding predisposing factors such as sunlight. However, current LES therapy prevents the patient's condition from recurring (flare) or worsening and complications occur, it is hoped that in the future LES therapy can improve the general condition of the patient so that the patient can recover easily due to LES.

Conclusion: A new therapy for SLE patients is needed for increasing quality life and maintenance health. Further research is needed in the new therapy of SLE to improve safety and health condition itself.

Keywords: SLE, autoimmune; therapy

Abbreviations: SLE: Systemic Lupus Erythematosus; AAV: Adeno-Association Virus; EAE: Experimental Allergic Encephalomyelitis; APS: Antiphospholipid Syndrome

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by the development of autoantibodies and immune complexes associated with a variety of clinical manifestations and tissue damage. SLE is one of several types of lupus, such as discoid lupus and drug induce lupus. SLE is the production of reactive antibodies against the body's own cells. SLE is multifactorial and most likely involves a complex interaction of genetic, environmental and hormonal factors. Several autoantibody specimens that contribute to disease either by binding directly to self-antigens or by induction of inflammation after deposition of a

network of antigen antibody immune complexes [1]. Immunological components that undergo functional changes play a role in the pathogenesis of SLE resulting in pathogenic autoantibodies, lack of T- and B-lymphocyte regulation and imperfect immune complexes. Autoantibody is a condition in which the antibody attacks itself. Autoantibodies found in lupus are directed at intracellular nucleoprotein partic SLE, with 98% of patients exhibiting antinuclear antibodies, while anti-double-stranded DNA antibodies are found in 50-80% of patients [2]. The prevalence of SLE is nine times more common in women, but the main cause of the sex differences has not been explained. The prevalence of SLE is 31 per 100,000 women in a population of European descent, which is 50-75% lower than in other populations. SLE predominantly affects women in a 9: 1 ratio. The prevalence of women is 90% in African Americans, compared to men [3].

The annual incidence of SLE in Europe is 3.3 per 100,000 population in Iceland and 4.8 cases per 100,000 population in Sweden. In America, however, the incidence of SLE has been investigated in various studies, ranging from 2.0 to 7.6 cases per 100,000 population. In Onikawa, Japan, a study identified 566 new cases with a diagnosis of SLE or 3.0 cases per 100,000 population. Meanwhile, studies on the prevalence of SLE show mixed results. This diversity is caused by differences in methods and socioeconomics. In Europe, the prevalence of SLE is 12.5 cases per 100,000 women, which is an increase in women aged 15-64 years. The prevalence of SLE in the United States shows a range of 14.6 to 50.8 cases per 100,000 population [2]. SLE is a multisystem autoimmune disease that can exacerbate and remit. This disease attacks various organs such as the skin, kidneys, musculoskeletal, nervous, cardiovascular, and oral cavities. As many as 50-70% of SLE patients have kidney problems. Renal involvement is a major cause of high morbidity and mortality in this population. Clinically, renal disease in SLE begins with asymptomatic proteinuria which then progresses rapidly to progressive glomerulonephritis with renal failure. About 95% of SLE patients can show musculoskeletal manifestations. Arthralgia, joint deformities, temporomandibular joint abnormalities and avascular necrosis have been reported in SLE patients [4]. Systemic lupus erythematosus (Systemic Lupus Erythematosus / SLE) cannot be cured, but there is a series of active phases (flares) and the calm phase of the disease. The goals of available treatment are to reduce the severity of symptoms, prevent organ damage, and minimize their impact on the life of people with SLE. The type of drug and dose given to one lupus sufferer is not the same as other lupus sufferers and can change from time to time depending on the symptoms you feel and the severity of them. Therapy in lupus is very individualistic depending on the severity of the disease, the goal is to suppress disease activity by weighing the risk of side effects. In life-threatening patients, therapy is carried out as aggressively as possible by administering very high doses of the drug and carried out in a hospital [1,2]. New therapy is needed in lupus patients so that life expectancy increases, and complications can be avoided.

Discussion

In recent years, the treatment of SLE nephritis has been based on several years of high doses of immunosuppressants and NSAIDs in mild cases. Immunosuppressants used can be metotrexan, corticosteroids, cyclophosphamide, cyclosporin A, azatiophrine and mycophenolate mofetil. This kind of approach is usually used in severe cases such as lupus nephritis by using several drug combinations. Another therapy for SLE is by changing the lifestyle (lifestyle) by maintaining health with exercise, diet and vitamins and avoiding predisposing factors such as sunlight. However, current SLE therapy prevents the patient's condition from recurring (flare) or worsening and complications occur, it is hoped that in the future SLE therapy can improve the general condition of the patient so that the patient can recover easily due to SLE [5].

Stem Cell Therapy

Some of the drawbacks of SLE therapy are targeting a specific pathway in the immune response, especially dysfunctional regulation occurring at several points. One of the successful cases in curing autoimmune especially and RA in the case after bone marrow transplant, but there is not much research on this matter. Cancer patients and clinical oncology cases, using immunoablation and high-dose cyclophosphamide, with autologous stem cell transplantation hematopoietic reconstitution (HSCT) have been used in autoimmune disorders with some success [6]. Cyclophosphamide is sometimes not always myeloablative as stem cells are resistant to its effects, high doses of this drug (50 mg / kg per day for 4 days) together with granulocyte colony-stimulating factor are useful in SLE patients. European data show, of the 50 patients who underwent autologous HSCT, 80% had partial or complete remission at 6 months, although 32% of these later relapsed. Immunoablation / HSCT could be a further improvement therapy to a procedure that can help reduce mortality rates [7].

Gene therapy

Gene therapy can change the expression of regulatory proteins or genes. Single-gene targeting does not always work for all SLE patients, except for a fairly rare cause such as a C4 deficiency, which can make the patient worse off. However, other targets such as IFN-γ, in lupuster mice are delayed onset and mild [7]. Another study used DNA transfection targeting cytokines to alter growth factor-β and IL-2, and as co-stimulation blockade with gene transfection of CTLA4Ig. A mouse model of the efficacy of gene transfer at work has been demonstrated in NZB / NZW lupus mice with adeno-association virus (AAV)-mediated gene transfer of CTLA4Ig or CD40Ig. The result was that when using the AAV serotype 8-CTLA4Ig reduced autoantibody production, proteinuria and a longer life span. However, gene therapy must be tested in humans, and further research is needed [8].

Intravenous immunoglobulin (IVIG)

IVIG is a blood product that is prepared from the plasma of several individuals. High doses of immunoglobulins have

immunomodulatory properties. The IVIG mechanism is an idiotype network, modulation of immune complex deposition and complement. IVIG also suppresses B lymphocyte activation by increasing the expression of Fc gamma receptors (FcγR) on B and DC cells. The interaction between Fc IgG and FcγR fragments on target cells is important for many anti-inflammatory effects and B cells. Cross-combining BCR to FcRIIB causes a decrease in antibody production [9]. There are no studies on the effectiveness of IVIG in SLE patients. Several reports of small clinical trials, case series, and case reports and literature support their use in SLE patients with arthritis, fever, thrombocytopenia, neuropsychiatric SLE, myocarditis, cardiac tamponade, end-stage kidney, chorea, polyradiculopathy, myelofibrosis, pneumonitis, membranous or membranoproliferative. lupus nephritis. There is a study that showed temporary beneficial effects on mild to moderate SLE. But IVIG therapy is an adjunct treatment for SLE and is an alternative therapy in difficult cases to treat SLE and cases with concomitant sepsis [10].

DNA Vaccination

DNA vaccination is being evaluated as a procedure to induce immune tolerance in autoimmune diseases. Vaccines rely on injecting genes encoding target proteins with the aim of eliciting a potentially tolerogenic immune response in the host. Vaccination DNA has successfully protected mice from organ-specific development in cases of autoimmunity, experimental allergic encephalomyelitis (EAE), autoimmune diabetes, experimental arthritis, experimental uveitis as well as SLE syndrome and antiphospholipids. Choosing the most appropriate vector for gene transfer is also an obstacle. The level of protection is influenced by the capacity of DNA vaccination to modulate the immune response affecting T helper cells and, T cell immunoregulation [7,8]. Evidence suggests that T cells that recognize consensus Ig sequences are formed by B cells and can modulate lupus in mice. NZB / W F1 lupus-rone mice fed B cells with plasmid DNA encoding consensus sequences of murine anti-DNA IgG can bind to Fc IgG or with plasmid control. The peptide conjugation with Ig in the Fc section provides structural stability to the peptide and localizes the transgenic constructs to the endosomes, enabling optimal processing and presentation. This approach efficiently protected mice from SLE, increased survival and reduced the severity of nephritis. Another study also demonstrated that the consensus expression of anti-DNA sequences induced immunoregulation of T cells with reduced disease expression [5].

Statins

As we have learned more about the immunomodulatory effects of statins, they have been evaluated as therapeutic agents for autoimmune diseases. Statins inhibit the production of proinflammatory mediators such as TNF-α, IL-1β, IL-6, IL-8, RANTES, monocyte chemotactic protein 1 (MCP-1), IL-17, cyclooxygenase 2, and nitric oxide by T and APC cells. Both in vitro and in vivo studies show that statins stimulate the secretion of Th2 cytokines, including IL-4, IL-5, IL-10, and alter the TGFβ factor. Statins also seem to suppress the transduction pathway of IFN and IFNγ- inducing the expression of histocompatibility complex class II (MHC-II) in various cell types [7]. Statin-induced repression of MHC-II also represses MHC-II-dependent activation of T cells. Statins also decrease costimulatory molecular expression and adhesion. Statins can also play an important role in the prevention of cardiovascular disease in SLE patients. In addition to their effect on suppressing choSLEterol synthesis, statins have an antithrombotic / anti-inflammatory effect in antiphospholipid syndrome (APS) patients. A controlled study has recently shown decreased SLE disease activity (SLEDAI) after atorvastatin therapy in addition to increased endothelial-dependent vasodilation in SLE patients after 8 weeks [9].

Monoclonal Antibodies

Monoclonal antibodies can specifically bind and neutralize the stimulator lymphocytokine B cytokines (BLyS), which is belimumab. Increased serum BLyS concentrations were found in a large proportion of SLE patients and correlated with anti-double-stranded DNA (anti-dsDNA) titers. BLyS (also known as B cell activation factor of the tumor necrosis factor (TNF) family, BAFF) is released by myeloid cells and activates B cells, maturation and production of antibodies especially at BAFF receptors, and effector T lymphocytes (Grech and Khamasta, 2014). BLyS also interacts with B receptor cell maturation antigen (BCMA) and transmembrane activator and CAML interactor (TACI), which mediates class switch recombination. Hence the overall inhibition of BLyS in B cell attrition and reduction of autoantibodies [9].

Targeting b-cell surface molecules

The use of off-label rituximab greatly exceeds belimumab in clinical practice, especially in patient's intolerant or unresponsive to standard care and with severe organ manifestations. Rituximab is a chimeric monoclonal antibody against CD20, a molecule on the surface of mature B cells. The effector cell Fc gamma (g) receptor, causing reduced effector cell-immune complex interactions, prevents subsequent inflammation and tissue injury. But a study shows twenty-two percent of patients experience side effects, of which mild infections are the most common [11].

Target co-stimulation molecules

Therapeutic approaches indirectly targeting B lymphocytes have recently been investigated. Helper T cells that mediate B cell activation, proliferation and class-switching require co-stimulation of signaling, where the interaction between CD40 and CD40L is essential. Studies show T cells from SLE patients express higher levels in CD40L. The study found that treatment with anti-CD40L antibody (BG9588) decreased anti-dsDNA titers and hematuria5.

The co-stimulatory interaction between CD28 (implied in T cells) and the B7 co-ligand is key in the activation and proliferation of B and T cells, providing an alternative therapeutic target in SLE. B7 is a fusion protein from the extracellular domain of cytotoxic T

lymphocyte antigen 4 (CTLA-4, homologous CD28) associated with the Fc portion of IgG1. The interaction of B7 as CTLA-4 binds to B7 with a higher affinity than CD287.

Cytokines

In addition to co-stimulation, many of the effectors and immunoregulatory functions of immune cells are mediated through cytokine production. IL-10, IL-6 and TNF-a (Ponticelli, 2006). IL-6 is a pleiotropic cytokine produced by activated monocytes, fibroblasts and T cells. It stimulates the differentiation of terminal B lymphocytes into mature plasma cells and induces growth and differentiation of T cells. As a growth factor, IL-6 also facilitates mesenchymal cell proliferation and could be a useful target in the proliferation of lupus glomerulonephritis. Indeed, IL-6 is highly expressed in the kidneys in lupus nephritis and urinary tract excretion correlates well with disease activity [7]. Tocilizumab is a monoclonal antibody that is targeted against the A-chain IL-6 receptor and is currently licensed for the treatment of rheumatoid arthritis. In the pilot study of tocilizumab in SLE patients, a significant reduction in anti-dsDNA and circulating plasma cells. ALSO-SLEDAI decreased from 4 in 50% of patients [9]. Studies have also shown interferon (INF) -a in the pathogenesis of SLE. Expression of peripheral blood profiling genes of mononuclear cells has revealed a large number of IFN-induced dysregulation in SLE compared to controls. The mechanisms employed by IFN-a. The pathogenesis of the disease is complex and multifactorial. It stimulates differentiation of B-cell germ centers and activation of dendritic cell maturation, which increases autoantigen presentation to T cells. IFN-a also exerts an inhibitory effect on regulatory T cells, which is fundamental in the maintenance of tolerance to self-antigens. IFN-a activates toll receptor (TLR) signaling in plasmacytoid dendritic cells, stimulating more IFN-production [8]. Furthermore, neutrophils in SLE undergo a high rate of cell death known as 'netosis', a process by which extracellular traps of neutrophils (NETs) are released into the circulation. NETs consist of DNA and neutrophil proteins, which readily stimulate plasmacytoid dendritic cells and IFN production. In this way, a positive IFN-gene feedback mechanism occurs. Sifalimumab is an anti-IFNa monoclonal antibody that blocks IFN signaling via the IFN-a / b receptor (IFNAR). Post hoc analysis revealed that significantly patients in the active group experienced flares (measured by SLEDAI) and required an increase in the dose of immunosuppressive agents [5].

Future therapeutic targets

A variety of biochemical T cell defects in SLE patients have been identified. In SLE patients, upregulation of the Fc receptor chain (FCR) T cells is associated with abnormal signaling via spleen tyrosine kinase (Syk). This pathway is associated with higher calcium ingress and hence stronger signaling, which may be related to the phenotypic characteristics of hypersensitive T cells in SLE. Fostamatinib is a Syk inhibitor, which has shown success in preclinical studies involving lupusprone mice. Currently there is no clinical trial of fostamatinib at the SLE, so further research is needed [8]. The inhibition of calcium-activated calcium-calmodulinkinase therapy (CaMKs) is currently being investigated for abnormal activation in SLE associated with IFN signaling via Jak and IL-2. Other immunomodulatory strategies including epigenetic modifications, antioxidants and tolerogenic peptides can be alternative SLE therapy [11].

Conclusion

A new therapy for SLE patients is needed for increasing quality life and maintenance health. Further research is needed in the new therapy of SLE to improve safety and health condition itself.

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