Traditional and Novel Treatments for Systemic Lupus Erythematosus

LIANG Yat Hei Cissy[1, *]

[1]Department of Life Science, Hong Kong University of Science and Technology, Hong Kong, China

*Corresponding author Email: yhcliang@connect.ust.hk

Abstract. Being one of the most complicated autoimmune diseases in the world, Systemic Lupus Erythematosus (SLE) has been researched for years, yet the underlying mechanism remains unclear. This literature review aims to provide a brief overview of SLE symptoms and complicated diseases, namely the formation of malar rash, arthritis, and multiorgan failure. Additionally, the pathogenesis of SLE will be discussed, analyzing the relationship between apoptotic clearance, adaptive immunity and SLE. Followed by an examination of various treatment methods. The effectiveness and safety of these treatments will also be evaluated. Furthermore, this review will explore the possibility of Stem Cell Therapy as a novel treatment for SLE. Cases of using stem cell therapy as a treatment for SLE will be studied and analyzed to determine its feasibility and potential risks. By critically reviewing published papers and recent studies, this literature review seeks to offer an introduction to the symptoms of the disease, assess the safety, effectiveness, and side effects of the current mainstream treatments, and propose stem cell Therapy as an innovative treatment to SLE.

Keywords: Systemic Lupus Erythematosus; Autoimmune disease; Lupus Nephritis; Belimumab (BLM); Stem Cell Therapy.

1. Introduction

Systemic Lupus Erythematosus (SLE) is one of the most devastating autoimmune diseases globally [1]. Due to the unique and non-clarified pathogenesis, SLE is considered to be a rare disease with limited treatments. The high prevalence of SLE is severely affecting childbearing females in different ethnicities [1]. The need for high effectiveness and high safety level treatments are crucial. Research on disease about Lupus has started since the 50s, many antibodies were suggested to be a treatment of lupus, but at the same time many are proof of lack of effectiveness and safety [2]. The potential side effects of traditional treatments should be monitored and controlled. Since the development of biotechnology has significantly evolved, Stem cell therapy is suggested to be a powerful treatment of different diseases [2]. More research can be done to investigate the effectiveness and the safety of this treatment.

Until now, the underlying cause of SLE is not fully understood and the treatments are mostly symptom curing instead of disease curing [1, 2]. Moreover, the side effect of current treatments was still under investigation. Since SLE is a highly heterogenous disease, it is worth researching the effect of different individuals be prescribed of the same kind of treatment. By understanding the genetic factor of pathogenesis of SLE and be able to identify the biomarkers would be effective for researchers and doctors to diagnosis, track and manage the disease, thus, treatments and patient care will be improved and optimized.

Till 2023, the SLE prevalence is over 7000 cases per 100000 individuals worldwide [3]. Studies also suggested that the prevalence of SLE will be increasing in later years [3]. This disease should be taken seriously due to the difficulty in diagnosis, the challenges of treatment and the low cure rate.

This literature review aimed to review the symptoms and complication diseases of SLE, to provide an overview of current treatment, and to discuss the advantages as well as the drawbacks of current treatment. Case studies of immunosuppressive drugs and Belimumab antibody treatment will be reviewed to evaluate the safety and effectiveness. In addition, this paper will review the feasibility, effectiveness and safety of stem cell therapy based on different research projects.

2. Clinical Manifestation of Systemic Lupus Erythematosus

In general, patients of early stage SLE experience fatigue, cold and loss of appetite, these symptoms are general that might lead to misdiagnosis and late diagnosis of the disease [1].

2.1. Malar Rash Across Face

Malar rash on nose and cheeks is one of the most significant symptoms on SLE patients, it is typically photosensitive, and the rash will be worsened under exposure to ultraviolet (UV) light [1, 4]. UV light radiation causes damage to keratinocytes and thus induces the release of cytokine [4]. SLE patients will show a hypersensitive response against cytokines [4]. This immune system activity leads to dilation of the blood vessels, resulting in the characteristic redness on the face.

2.2. Arthritis

Arthritis can be considered as both a symptom of SLE and a complication disease induced by SLE. Early-stage arthritis is characterized as joint swelling, pain and stiffness [1, 2]. At this stage, most cases could be diagnosed as osteoarthritis, by prescribing painkillers such as Acetaminophen, which has limited anti-inflammatory effects, might aggravate SLE.

2.3. Multiorgan Tissue Damage

2.3.1. Kidney Failure Caused by Lupus Nephritis (SLE-LN)

Lupus nephritis as a high prevalence complication induced by SLE, with a 50% incidence, the pathogenesis should also be emphasized [2]. Symptoms of Lupus nephritis are proteinuria, microscopic hematuria, tubular urine and kidney failure [5].

2.3.2. Brain Damage Caused by Neuropsychiatric Systemic Lupus Erythematosus (SLE-NL)

Neuropsychiatric Lupus is also a high prevalence complication induced by SLE, with a 46% incidence, this disease should also be taken seriously. The symptoms of SLE-NL are seizures and cognitive and memory impairment due to the inflammation in the brain area [2]. There is a certain chance that patients are also diagnosed with aseptic meningitis, meaning that the inflammation in the meninges is not induced by bacteria or virus, instead, it is induced by the autoinflammatory process associated with SLE. The pathogenesis of SLE-NL is not clear yet [2]. However, studies showed that this disease might be triggered by cerebrovascular damage, damage in blood-brain barrier and injury in the brain [2].

2.3.3. Damage in Heart, Lungs and Blood Vessels

There are a variety of involvement of heart and lungs in SLE patients, such as pulmonary arterial hypertension (PAH), pulmonary and vascular lesions caused by autoinflammation response in heart, lungs and blood vessels [1, 2]. In particular, SLE-PAH is the main cause of mortality of SLE, because of its difficulties in diagnostics at the early stage [2]. In addition, inflammation in the heart also causes diseases such as myocarditis, which occurs in the heart muscle, and pericarditis, which occurs at the membrane surrounding the heart [1, 2].

As a short conclusion, most of the symptoms and complication diseases are caused by the disorder and misregulation in the immune system, body cells release pro-inflammatory cytokines to induce the immune cells to attack healthy tissue in different organs, injuries in different organs triggers more severe immune response, cytotoxic cells mistakenly attack healthy tissue, since the injuries were not caused by bacteria or parasite. This causes a vicious cycle in patients and results in multiorgan failure.

3. Pathogenesis

SLE is triggered and aggravated by a variety of factors, it is known for the difficulty to track the pathogenesis and the followings are some known etiologies of SLE. However, it is believed that the cause of SLE is closely linked to the dysfunction and misregulation in apoptotic clearance [6, 7].

3.1. Apoptotic Clearance

Apoptotic clearance refers to the clearing of programmed death cells, the importance of the process is to maintain the homeostasis of tissue and prevent inflammatory response. During apoptosis, cells shrink and lyse, and form apoptotic bodies. These apoptotic bodies display specific "eat-me" signal protein on their surface, such as phosphatidylserine (PS) will act as recognition markers for phagocytes [6]. Phagocytes once recognized the protein on the apoptotic cell surface, they bind to and engulf the apoptotic cells. The apoptotic cell is then enclosed within a phagosome, which fuses with lysosomes to form a phagolysosome. And within the phagolysosome, the apoptotic cell is degraded, and its components recycled or eliminated [6].

3.1.1. The Dysfunction of Apoptotic Clearance

Defects in apoptotic clearance can lead to the accumulation of apoptotic cells. This result in prolonged exposure of cells to apoptotic cell-derived factors, such as damage-associated molecular patterns (DAMPs) and pro-inflammatory molecules, such as TNF-α and IL-6 from phagocytes, that could activate and further amplify the immune response [6]. The accumulation of apoptotic cells can trigger overreactive immune response. In addition, the presence of accumulated apoptotic cells contributes to the development of autoimmune responses, as the immune system may recognize self-antigens present on apoptotic cells.

3.1.2. Impaired Immune Tolerance

Dysfunction of Apoptotic clearance lead to impaired immune tolerance, since apoptotic clearance plays a crucial role in maintaining immune tolerance by promoting anti-inflammatory signals and immunosuppressive responses [6]. When apoptotic clearance is defective, the balance between pro-inflammatory and anti-inflammatory signals is disrupted [6]. This can lead to the loss of immune tolerance, contributing to the induction of SLE.

3.2. Adaptive Immunity

3.2.1. B-lymphocyte and Autoantibodies

The maturation of B-lymphocyte is induced by B-cell activating factor (BAFF), the overexpression of BAFF can abnormally activate B-lymphocyte and induce the production of autoantibodies. This leads to the production of autoantibodies and the dysregulation of the immune response. The exact mechanisms of abnormal B-lymphocyte activation and expression are unclear, but it involves genetic and environmental factors.

B-lymphocyte became dysregulated and produce autoantibodies. Mature B-Lymphocytes are responsible for producing antibodies, the abnormal engagement of toll-like receptor (TLR), promote the production of autoantibodies. These autoantibodies work against double stranded DNA and RNA. These antibodies will form complexes with antigens and cause autoinflammation that would lead to internal organ damage and induce SLE.

B-Lymphocytes produces pro-inflammatory cytokines, such as IL-6 and TNF- α. The overexpression of B-lymphocyte caused the overexpression of cytokines, which contribute to the severe inflammation.

3.2.2. T-lymphocyte Relationship and Regulation

T-lymphocyte act as an important role in the pathogenesis of SLE, it triggers the release of many pro-inflammatory cytokines and suppress the release of anti-inflammatory cytokine. Studies show that SLE patients has a misrelated T-lymphocyte expression, the T-helper 1 Cells (Th1) increased to induce the oxidation of IFN-γ thus aggravate SLE. At the same time, the number of T-helper 2 cell, which is potentially protective against SLE, decreased. In addition, T-helper 17 cells, which release pro-inflammatory IL-17, also increased in blood. In contrast, studies showed that regulatory T cells (Treg) were decreased in blood of SLE, revealed that Treg have difficulty in regulating the expression of T cells in SLE patient, and the underlying reason is multi-factorial. Some potential reasons of dysfunction of Treg such as impaired Treg- T cell effector balance and altered Treg phenotype.

4. Treatments

4.1. non-specific therapeutic agents

Glucocorticoids is a commonly used steroid treatment on SLE, it inhibits the activation and proliferation of B-lymphocyte and T-lymphocyte, thus suppress the production of SLE inducing pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-alpha [2]. This helps reduce the inflammatory response and attenuate the immune response. In addition, by suppressing B-Lymphocyte activity, the production of autoantibodies is reduced [8].

4.1.1. Mechanism

When glucocorticoids enter immune cells, they bind to cytoplasmic glucocorticoid receptors [9]. This binding causes a conformational change in the receptor to activate. The activated receptor will migrate to the nucleus and bind to glucocorticoid response elements [9]. At the same time, the activated receptors directly inhibit the expression of immune cells.

4.1.2. Safety Concerns

The side effect of taking steroid medication should also be considered to evaluate the safety of the treatment. Some potential risks such as increased potential if getting an infection, osteoporosis and neurological or mental illness [6]. Taking glucocorticoids might inhibit bone formation and decrease calcium absorption in SLE patients [10]. Some patients might also experience neurological or mental illness after taking Glucocorticoids medications [10].

4.2. Biological Antibodies

Belimumab (BLM), one of the major treatments of SLE [2, 6]. It is also the first SLE treatment approved by FDA [6].

4.2.1. Mechanism

Belimumab targets on BAFF, so that the maturation and proliferation of B-lymphocyte will be suppressed. By binding to BAFF, BLM prevent the interaction of BAFF and its receptor (BAFF-R), so that the signaling of B-lymphocyte proliferation will be suppressed and, therefore, the autoimmune response and symptoms of SLE patients can be alleviated [11].

4.2.2. Data and Safety Concerns

Multiple research projects showed that BLM has significant effect on SLE patients, at the same time, the safety is also examined by researchers. Since 2001, two Belimumab treatments (BLISS-52 and BLISS-76) started their stage three clinical trial on SLE patient with LN complication [6, 11]. According to their result, the BLM treatment group have a better renal health response compared to patients accepting glucocorticoids treatment and the placebo group [11]. This also reflect that the safety and efficiently of BLM treatment on SLE and LN.

However, according to a BLM review in 2020, studies also shows that there is positive correlation between BLM treatment and severe mental illness and neurological diseases, such as progressive multifocal leukoencephalopathy and severe depression [12]. Awareness should be raised, and more research should be done in order to analyze the effect of BLM on neurological diseases and mental illness.

4.3. Stem Cell Therapy

As the rocketing improvement in biotechnology, many novel treatments were suggested. One of the most mentioned treatments is stem cell therapy.

4.3.1. Case Studies

In 2017, Doctors in Beijing Union Medical College Hospital performed a peripheral blood stem cell therapy on 18 SLE patients and promising outcomes showed that Stem cell therapy have the potential to become one of the advanced treatments of SLE [2]. With the immunosuppressive drug

treatment, they discovered that peripheral blood stem cell therapy is a practical novel treatment with relatively high safety. The follow-up examinations showed that the survival rate of patients is improved [2].

In 2020, a research team also discovered that mesenchymal stem cells (MSCs) have a significant effect on immunoregulation by performing experiments on mice [13]. SLE model mice accepting MSCs treatment reflects a lower B-lymphocyte and cytotoxic T-cell in spleen, compared to the untreated mice [13]. In addition, the hair loss, skin ulcers, proteinuria of mice in the treatment group were significantly lower than those in the untreated group [2, 13].

4.3.2. Concerns

Despite the fact that stem cell therapy has highly promising outcomes, the potential risks of stem cell therapy should also be addressed. Stem cell therapy might involve the use of autologous stem cells or allogeneic stem cells [13]. In case of allogeneic stem cell therapy, the potential risk is that the SLE patient's immune system recognizes the transplanted cells as foreign, triggering an immune response, causing rejection response. Additional immunosuppressive medications may be required to reduce this risk. In addition, stem cells are known for being able to self-renew and differentiate into different cell types. However, there is a potential risk of uncontrolled cell growth and caused tumor formation if stem cells have not been properly characterized. Quality control measures and multiple stages of clinical testing are essential to minimize this risk.

The underlying ethical problem of performing stem cell therapy should also be noticed. For instance, stakeholders have been arguing on the use of embryonic stem cells for culturing new cells and even organs. Under the circumstance that the regulations are unclarified, stem cell therapy cannot be a commonly used treatment.

5. Conclusion

Through reviewing different sources, it is encouraging to know that the research on SLE has been emerging. Although SLE is a heterogeneous disease, the understanding of the underlying mechanism and pathogenesis is deeply investigated, and many possibilities are found. As the understanding of the disease gains, more biological antibodies treatments targeting different biomarkers are being investigated and developed. The ultimate aim is to guarantee the safety and effectiveness of the treatment and it is hopeful that the improvement in immunology field and medical field can improve the quality of life of SLE patients. As mentioned in the review, the results of stem cell therapy in SLE are promising, yet more case studies should be done to examine its side effects, there is still a long way to go before accepting stem cell therapy as a regular treatment.

To conclude, SLE is a complicated disease, the improvement in technology and knowledge can definitely help scientists, doctors and patients understand the disease. The innovation in technology also enables the improvement in treatments of SLE, and hopefully these improvements would enhance the quality of life for SLE patients.

References

[1] NIAMS. Systemic Lupus Erythematosus (Lupus) [Internet]. National Institute of Arthritis and Musculoskeletal and Skin Diseases. 2019 [cited 2024 Mar 17].

[2] Jiang N, Bai W, Zhao J, et al. Diagnosis and treatment directions and research frontiers of systemic lupus erythematosus. SCIENTIA SINICA Vitae, 2021, 51(8): 887–900.

[3] Barber M R W, Falasinnu T, Ramsey-Goldman R, et al. The global epidemiology of SLE: narrowing the knowledge gaps. Rheumatology, 2023, 62(Supplement_1): i4–i9.

[4] Barbhaiya M, Hart J E, Malspeis S, et al. Association of Ultraviolet B Radiation and Risk of Systemic Lupus Erythematosus Among Women in the Nurses' Health Studies. Arthritis Care & Research, 2023, 75(7): 1409–1415.

[5] Lech M, Anders H-J. The Pathogenesis of Lupus Nephritis. Journal of the American Society of Nephrology, 2013, 24(9): 1357–1366.

[6] Accapezzato D, Caccavale R, Paroli M P, et al. Advances in the Pathogenesis and Treatment of Systemic Lupus Erythematosus. International Journal of Molecular Sciences, 2023, 24(7): 6578.

[7] Lisnevskaia L, Murphy G, Isenberg D. Systemic lupus erythematosus. The Lancet, 2014, 384(9957): 1878–1888.

[8] Tanaka Y. State-of-the-art treatment of systemic lupus erythematosus. International Journal of Rheumatic Diseases, 2020, 23(4): 465–471.

[9] Kamhieh-Milz J, Ghosoun N, Sterzer V, et al. Effect of glucocorticoid treatment on BAFF and APRIL expression in patients with immune thrombocytopenia (ITP). Clinical Immunology, 2018, 188: 74–80.

[10] Tavares L C P, Caetano L D V N, Ianhez M. Side effects of chronic systemic glucocorticoid therapy: what dermatologists should know. Anais Brasileiros de Dermatologia, 2024, 99(2): 259–268.

[11] Felten R, Lipsker D, Sibilia J, et al. The history of lupus throughout the ages. Journal of the American Academy of Dermatology, 2022, 87(6): 1361–1369.

[12] Ke Lin, Dong Lei, Li Yue-qiang, et al. Clinical efficacy and safety of belimumab for lupus nephritis:a clinical observational study[J]. Journal of Clinical Nephrology, 2023, 23(2): 124-128.

[13] Li A, Guo F, Pan Q, et al. Mesenchymal Stem Cell Therapy: Hope for Patients with Systemic Lupus Erythematosus. Frontiers in Immunology, 2021, 12: 728190.