Eurasian J. Sci. Eng., 2023, 9(2), 231-240
https://doi.org/10.23918/eajse.v9i2p18

Published by Tishk International University
Available at: https://eajse.tiu.edu.iq/

RESEARCH ARTICLE Open Access

UNRAVELING THE LINK BETWEEN LYMPHOPENIA AND SYSTEMIC LUPUS ERYTHEMATOSUS: IMPLICATIONS FOR DISEASE SEVERITY AND POTENTIAL TREATMENT STRATEGIES

Sawsan S. Al- Rawi [1*], Ahmad H. Ibrahim [2], and Gasheen B. Ahmed [1]

[1] Biology Education Department, Faculty of Education, Tishk International University, Erbil, KRG, Iraq.

[2] Department of Pharmacy, Faculty of Pharmacy, Tishk International University, Erbil, KRG,Iraq.

Article History
Received: 13.03.2023
Revised: 13.06.2023
Accepted: 20.06.2023
Communicated by: Dr. Orhan Tug
*Email address:
sawsan.hamed@tiu.edu.iq
*Corresponding Author

Abstract:
Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by chronic inflammation that can potentially impact any body part. Lymphopenia, abnormal low lymphocyte numbers, are frequently observed in individuals with active SLE. This short review examines the correlation between lymphopenia and SLE. Databases of Scopus, PubMed, Elsevier, Wiley, and Google Scholar were searched for related publicationS. The results showed that lymphopenia is correlated with disease severity in SLE patients. The underlying mechanism is unclear, but it may be due to increased apoptosis of lymphocytes and the autoantibodies production that target lymphocyte surface receptors. Various therapies, including immunosuppressive, corticosteroids, and antiangiogenic agents, have been used for SLE management. However, their efficacy is varied in SLE patients with lymphopenia. These therapies may improve lymphocyte counts and disease vigorousity. Lymphopenia has been found to be linked with several factors in SLE patients, including lupus nephritis, higher steroid doses, cyclophosphamide uses and complement depletion. In SLE, abnormal angiogenesis has been linked to the disease pathogenesis. Thus, angiogenesis therapy for SLE selectively targeted the process of abnormal blood vessel growth that is associated with SLE. In summary, lymphopenia may serve as an indicator of disease severity, however, further studies are required to explore the efficacy of targeted and non-targeted therapies in managing SLE patients with lymphopenia.

Keywords: *Autoimmune; Systemic Lupus Erythematosus; Lymphopenia, Immunosuppressive; Corticosteroid; Steroid; Angiogenesis; Therapy.*

1. Introduction

SLE (systemic lupus erythematosus) is a chronic autoimmune disease that can potentially affect and harm any body part or tissue including the skin, joints, kidneys, heart, and lungs [1]. During the development of the disease, several factors play a key role, including, hormonal milieu, environmental causes, and genetics [2]. The complex interplay of modified molecular pathways that lead to the clinical phenotype of SLE results in a diverse range of symptoms and patterns of organ involvement [3]. During a flare, a person with SLE may experience symptoms such as joint pain, skin rash, fever, fatigue, muscle aches, and inflammation in various organs. These symptoms can be mild or severe and can last for days or weeks. Flares can be unpredictable and can occur at any time, even when a person's SLE has been well-controlled. The pathogenesis of SLE involves various cellular components of the

innate and immune systems, the presence of autoantibodies and immune complexes, activation of the complement system, dysregulation of cytokines (including type I interferons), and impaired clearance of nucleic acids following cell death [4]. The ratio of SLE occurs more often in women with a ratio of 10 females to 1 male, particularly during their reproductive years [5]. Since, SLE disease has a broad range of changes, it can lead to a variety of clinical presentations that differ from one patient to another and affect virtually all organs and tissues. This will cause severe symptoms that threaten the health of various organs. As a result, early detection and treatment are critical, as a delay in diagnosis might result in damaging the body organs [6]. Although the exact cause of SLE is still unknown, and its pathogenesis is still not fully understood, however, CD4+ T lymphocytes have been implicated in the disease because of their critical function in giving helper signals that stimulate B cell differentiation into autoantibody production [7]. In addition, lymphopenia is a common observation in patients with active SLE [8]. Lymphopenia is a condition characterized by abnormally low lymphocyte numbers. This condition is uncommon among children and more common in the elderly [9]. Moreover, the elevated ratios of neutrophils to lymphocytes, monocytes to lymphocytes, and cytokine levels (including IL-2R and its ratio to lymphocyte count) have been associated with disease severity and an unfavourable prognosis in SLE [10]. Lymphopenia was found in 90% of lupus patients across the course of the disease [11]. Lymphopenia induces a temporal breakdown in the patient's immunologic tolerance, resulting in inflammation and the multiplication of peripheral T cells, which is an extra risk factor for the autoimmune disease's development [12, 13]. Except for infection prophylaxis, which should be individualized to the person, no specific guidelines for the therapy of SLE with lymphopenia have been made [14]. Therefore, the purpose of this paper is to provide a comprehensive review of the most recent studies and findings related to the relationship between lymphopenia and systemic lupus erythematosus, as well as the latest potential targeted and non-targeted therapy approaches for treating SLE.

2. Method and Data Collection

In this short review, the search for published articles was conducted across multiple databases, including PubMed, Google Scholar, Scopus, Wiley, Science Direct, Elsevier, and Hindawi. The search for terms included systemic lupus erythematosus, symptoms, lymphopenia in SLE, pathogenesis of SLE, targeted and non-targeted therapies for SLE, and recent development in SLE therapy. Excluded criteria were the articles that are not published in English, theses, online sources, and literature review articles. The collected data were described and explained in the text.

3. Result and Discussion

3.1 The Correlation of Lymphopenia with Systemic Lupus Erythematosus

Lymphopenia is considered as the most common remark in patients with active SLE. However, the mechanisms underlying lymphopenia in SLE are not completely understood, but it is thought to involve multiple factors such as impaired lymphocyte production, increased lymphocyte destruction, and altered lymphocyte distribution. Lymphopenia in SLE patients may be more than a laboratory result, as it has been linked to lupus nephritis, complement proteins depletion, greater doses of steroids, and cyclophosphamide treatment [2]. In 2020, a study was conducted to examine the potential correlation between lymphopenia and various clinical manifestations, laboratory findings, disease activity, and damage index in patients diagnosed with systemic lupus erythematosus (SLE). The study involved the assessment of the systemic lupus international collaborating clinics damage index (SLICC-DI) and the SLE disease activity index (SLEDAI), as well as a comparison of the clinical characteristics of the patients [3]. Renal involvement was found in (69.4%) of SLE patients,

complement C3 was found in (67.7%), while complement C4 was found in (35.5%) patients [6]. Moreover, the researchers confirmed that Lymphopenia is a common finding in SLE patients, and it has been linked to lupus nephritis, higher steroid dosages, cyclophosphamide consumption and complement protein depletion. Complement consumption or depletion refers to the activation and consumption of complement proteins that are part of the immune system's defence mechanism. In SLE, the complement system may become overactivated, leading to excessive consumption of complement proteins, and contributing to disease pathology. Lymphopenia could be a useful indicator of renal involvement in SLE [2]. However, further investigations are still needed to ascertain whether lymphopenia is a sign of kidney flare or only linked to it and to find the relationship between lymphopenia and other SLE clinical characteristics [15]. In 2018, another study was conducted to study the relation of lupus nephritis with disease activity [16]. The study suggested that Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are two markers of inflammation can be used to evaluate the level of disease activity in individuals with SLE [17]. NLR may also show renal association in SLE patients and is linked to the various histological staging groups [11]. It was suggested that the decreased levels of splicing factor SRSF1 was due to Lymphopenia in SLE [18]. Recent article in 2020, clarified the effect of Splicing factor SRSF1 in the management of T cell homeostasis and its decreased concentrations due to lymphopenia in SLE [19]. The researchers suggested that the reduction of SRSF1 in T cells of patients with SLE is linked to the severity of the disease and may be responsible for causing lymphopenia. This is because SRSF1 is involved in regulating T cell homeostasis by controlling genes related to apoptosis. The unique functions of SRSF1 in cytokine signalling and production in T cells make it a potential target for future research and treatment strategies in SLE patients [19]. However, T cell lymphopenia was caused by selective deletion of Srsf1 in mice, which resulted in enhanced apoptosis and reduced the expression of the anti-apoptotic Bcl-xL. On the other hand, low SRSF1 expression was correlated with decreased levels of Bcl-xL in T cells, and low levels of Bcl-xL in patients with systemic lupus erythematosus (SLE) were linked with lymphopenia [20]. In November 2021, a study aimed to evaluate the correlation of the disease activity and use of medication with leucopenia (lymphopenia and neutropenia) in a worldwide, prospectively followed SLE cohort [21]. Neutropenia was found to be linked to the use of methotrexate (MTX) and ciclosporin medicine. Both lymphopenia and neutropenia were found to be negatively linked with the low disease activity stage of lupus. In addition, in SLE patients, Lymphopenia and neutropenia were both common although they were linked with illness and therapy factors in different ways [22]. Moreover, Lymphopenia was linked to the overall activity of the disease, ESR, prednisolone, serology, azathioprine (AZA), MTX, cyclophosphamide (CYC), tacrolimus and rituximab use in multivariable analyses [23].

3.2 Non-Targeted Therapies for SLE

Up to date, there is no cure for SLE, however, pharmacological treatment relies on the non-targeted therapies for systemic lupus erythematosus (SLE). It includes conventional immunosuppressive agents, such as glucocorticoids, antimalarials, and immunosuppressants, which are the mainstay of therapy for SLE as they can reduce organ damage and control the disease activity [24]. Glucocorticoids are potential anti-inflammatory agents that are used to control the acute manifestations of SLE [25]. They reduce endothelial cell permeability and suppress the synthesis of inflammatory cytokines while also preventing leukocyte recruitment [26]. However, they are associated with significant adverse effects, including infections, metabolic disturbances, and osteoporosis [27]. On the other hand, antimalarials, such as hydroxychloroquine, have been shown to decrease the activity of the disease and reduce the risk of flares in SLE patients [27]. Managing flares is an important part of SLE treatment, and it usually involves adjusting medications and making lifestyle changes to reduce triggers and

manage symptoms. Immunosuppressants, such as azathioprine, mycophenolate mofetil, and cyclophosphamide, are used in patients with more severe disease manifestations or those who do not respond to other therapies [28]. Non-steroidal anti-inflammatory drugs, such as hydroxychloroquine, are another possibility for treating SLE. However, these therapies can have unintended consequences, including lymphopenia. Lymphopenia is a common side effect of non-targeted therapies for SLE, such as corticosteroids, immunosuppressants, and cytotoxic drugs [29]. Lymphopenia was more common in SLE patients treated with high-dose corticosteroids compared to those treated with low-dose corticosteroids or non-corticosteroid therapies [30]. Moreover, lymphopenia was a common side effect of mycophenolate mofetil, an immunosuppressant drug, and was associated with a higher risk of infections, especially in patients with severe lymphopenia [31]. Therefore, it is important for clinicians to monitor lymphocyte counts regularly and adjust treatment accordingly to minimize the risk of lymphopenia-related complications.

3.3 Targeted Therapies for SLE

The treatment of SLE has traditionally involved non-targeted therapies, such as corticosteroids and immunosuppressants. However, there has been rising interest in developing targeted therapies for SLE in recent years [32]. Targeted therapies aim to specifically target the pathogenic mechanisms of SLE, while minimizing the off-target effects associated with non-targeted therapies. This is owing to the disease's complexity and different presentations [33]. T-cell regulation, B-cell modulation, and cytokine inhibition are three strategies used to develop biological therapy for the condition [34]. There are multiple potential therapeutic targets for systemic lupus erythematosus (SLE) within both the innate and adaptive immune systems, including B-cells, T-cells, interferon (IFN), and cytokines [35, 26]. One such target falls under B-cell therapy, which has led to the approval of belimumab as a treatment for SLE. Belimumab is a monoclonal antibody that specifically targets the B-cell activating factor (BAFF) receptor. BAFF is a cytokine that plays a critical role in B-cell survival and maturation. Elevated levels of BAFF have been seen in patients with SLE and are associated with disease activity [36]. Belimumab has been shown to reduce disease activity and improve patient outcomes in clinical trials [37]. Another targeted therapy for SLE is a monoclonal antibody that targets CD20, which is known as rituximab, and it is a surface antigen of B-cell. Rituximab has been shown to deplete B cells and is effective in reducing disease activity in SLE patients [38]. Lymphopenia is caused by a variety of reasons, including infections and drugs such as corticosteroids and cytotoxic agents (drugs that are used widely to treat LSE). Treatment for SLE is available in the form of B-cell, T-cell, and ant cytokine treatments. Antibodies and antigen interactions are important in these therapies [26]. Antibodies targeting CD8+ T lymphocytes, excessive apoptosis, and increased complement-mediated cytolysis of T cells, and defective lymphopoiesis and lymphocyte sequestration are among the pathophysiological processes of lymphopenia [12]. One of the proposed strategies of potential therapeutic value is to use special agents to modulate B cells. This strategy in targeting cytokines and B-cell surface antigens, to stimulate the functions and development of B-cell, and the interactions between Band T-cell as shown in (Fig. 1) which is adopted from Chen et al., [39]. This strategy offers some more promising future hope to treat SLE.

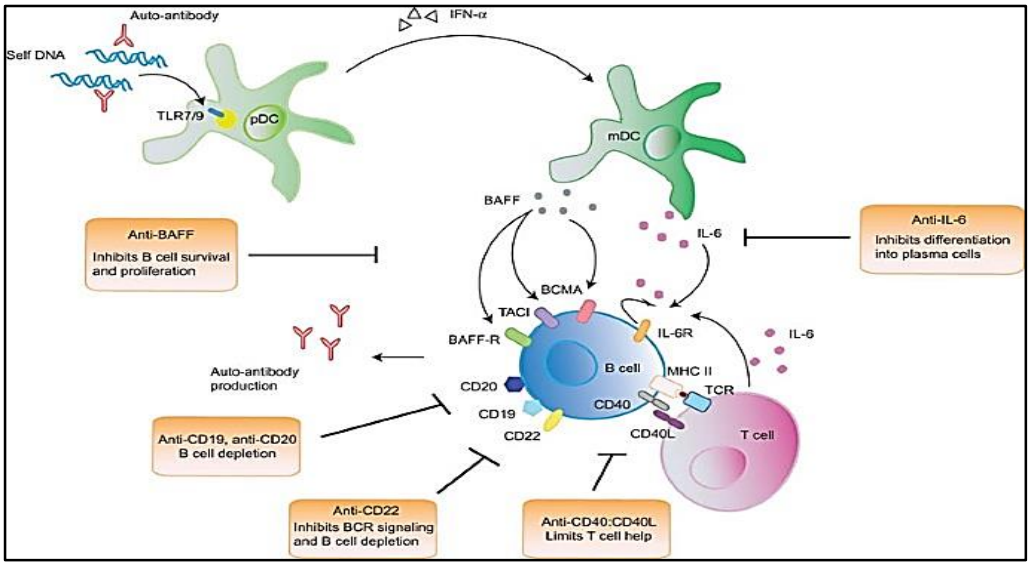

Figure 1: Shows a strategy to target the cytokines and B-cell surface antigens, to stimulate the development and functions of B-cell, and the connections between B and T-cell (Chan et al., 2013).

3.4 Angiogenesis as a Targeted Therapy for Treating Systemic Lupus Erythematosus

The targeted therapies have been designed to focus on certain molecules or pathways associated with the formation or progression of the disease. Angiogenesis therapy is an emerging approach that targeting diseases that are related to inflammation such as cancer, rheumatoid, wound healing, and cardiovascular disease by targeting abnormal blood vessel growth [40, 41]. Angiogenesis is a known process that targeting the formation of new blood vessels from existing ones, and it plays a critical role in tissue repair and regeneration [42, 43]. In SLE, abnormal angiogenesis has been linked to the disease pathogenesis, including the development of skin lesions, kidney disease, and vascular complications [44]. SLE is characterized by inflammation, which is related to the activation of pro-inflammatory signaling pathways, including those that promote angiogenesis such as VEGF [45]. The persistent inflammation that occurs in SLE is hypothesized to be connected to angiogenesis dysfunction [46]. It has been reported that an increase in angiogenic factors such as vascular endothelial growth factor (VEGF) was observed in SLE patients. These substances are produced by immune cells and have the potential to encourage the formation of new blood vessels, which may contribute to the development of SLE-related problems such as renal disease and skin lesions [47]. In addition, autoantibodies against angiogenic factors, such as anti-VEGF antibodies, have been found in SLE patients [48]. Thus, in SLE, the angiogenesis therapy precisely targets the process of aberrant blood vessel development that is linked with the disease [49]. However, several potential strategies using angiogenesis therapy have been investigated in recent years for treating SLE. One of these strategies is the use of substances to inhibit the production of angiogenic factors, such as (VEGF), which encourage the formation of new blood vessels [50]. Moreover, several VEGF-targeting medications are being evaluated in clinical trials for SLE and have previously received approval for use in treating other illnesses [50]. Another approach therapy, is targeting inflammation, a key feature of SLE, which also correlated with angiogenesis, such as the use of corticosteroids, a common SLE treatment, have been found to have anti-VEGF impact and anti-angiogenic activity [52]. Non-targeted medicines, on the other hand, function more broadly and affectively on a broader spectrum of cells or molecules. Nonsteroidal anti-inflammatory medicines (NSAIDs), for example, are a non-targeted treatment that can be used to reduce inflammation in SLE, but they do not explicitly address the underlying illness processes [53].

Therefore, it can be said that angiogenesis therapy a targeted therapy for SLE is selectively targeting the process of abnormal blood vessel growth that is associated with SLE. Overall, it can be said that angiogenesis targeted therapy appears to be a promising potential method that can be used for the treatment of SLE. However, further studies are still needed to fully understand its fundamental mechanisms and to set up the safety dose and effectiveness in clinical trials.

3.5 Combination Therapies for SLE

While targeted and non-targeted therapies have been commonly used, recent studies have explored other combination therapies that may be used to manage SLE. Combination therapies involving two or more medications are often used to improve disease control and reduce symptoms [54]. Recently, several studies have investigated different combination therapies for SLE. For instance, Furie (55) highlighted the importance of combination therapy in lupus nephritis. Immunosuppressive agents such as azathioprine, methotrexate, mycophenolate mofetil, and cyclophosphamide are used in combination with corticosteroids to suppress the immune system and prevent disease flares (56). Biologic agents such as belimumab, rituximab, and abatacept target specific parts of the immune system and are used to reduce disease activity in SLE (57). They may be used in combination with immunosuppressive agents to achieve better disease control (58, 55). Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to reduce pain and inflammation in SLE while antimalarials such as hydroxychloroquine are also used to reduce inflammation and prevent disease flare. These medications may be used together to control symptoms and prevent disease flares (58). Plasmapheresis is a procedure in which plasma is removed from the blood and replaced with other fluids. It is sometimes used in SLE to remove antibodies that are causing damage to the body (59, 60). Plasmapheresis may be used in combination with immunosuppressive agents to achieve better disease control (61, 62). It is important to note that combination therapies for SLE should be individualized based on the patient's specific disease manifestations, comorbidities, and response to treatment.

4. Conclusion

In conclusion, lymphopenia is a common feature of Systemic Lupus Erythematosus (SLE) and serves as a prognostic marker for the disease severity. The depletion of lymphocytes is believed to play a significant role in the pathogenesis of SLE. Both targeted and non-targeted therapies can be used for the management of SLE. Targeted therapies, such as B-cell depletion, have shown promising results in improving lymphopenia and reducing disease activity. Non-targeted therapies, such as immunosuppressive agents, have also been used in the management of SLE, they may have severe adverse effects. Further studies are needed to understand the mechanisms underlying the lymphopenia in SLE and to develop more effective and safe treatment strategies for patients with this disease. Ultimately, the understanding of the pathophysiology of SLE, will clear the path for more targeted and personalized therapies to become available to provide a better quality of life for those affected by SLE.

5. Author’s Contribution

We confirm that the manuscript has been read and approved by all named authors. We also confirm that each author has the same contribution to the paper. We further confirm that the order of authors listed in the manuscript has been approved by all authors.

6. Conflict of Interest

There is no conflict of interest for this paper

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