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Mechanism and Target Therapy of Rituximab in Systemic Lupus Erythematosus: Literature Review

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ABSTRACT

The malignant condition known as lymphoma affects the lymphoid tissues, bone marrow, and blood. Between 2009 and 2013, the incidence rate of lymphoma in the United States was approximately 22 per 100,000 individuals. Hemolytic anemia, leukopenia, and thrombocytopenia are among the hematologic symptoms of systemic lupus erythematosus (SLE), a highly diverse disease. Rituximab (RTU) and other monoclonal antibodies that target β cells are used as off-label therapy for SLE. Rituximab is a human CD20-specific chimeric monoclonal antibody. Rituximab can be utilized as an alternate therapy for SLE in addition to providing treatment for lymphoma. Rituximab has demonstrated positive effects and potential as a treatment for SLE in several clinical trials. This study aims to elucidate the mechanism of action of rituximab as a therapeutic agent targeting β cells in patients with SLE. The methodology used in this study is a literature review. The literature retrieval and search strategies were conducted using electronic means. A literature review of seven periodicals was produced by employing keywords to retrieve scientific material using the Boolean approach. Rituximab depletes and inhibits the activation of β cells in individuals with systemic lupus erythematosus by binding to the Fc gamma IIβ receptor on both β cells and macrophages.

INTRODUCTION

Since 1994, the WHO has categorized lymphoma as a tumor of the blood, bone marrow, and lymphoid tissues; this classification was revised in 2008. Two primary principles for diagnosing lymphoma were the basis for the 2008 update on the classification of lymphoid neoplasms: the categorization of neoplasms based on the origin of precursor or mature cells and cell lineage, as well as clinically significant different illnesses. A mix of morphology, immunophenotype, genetic factors, molecular features, and clinical characteristics are used to identify illnesses (Shen & Terezakis, 2020).

The chronic autoimmune disease known as systemic lupus erythematosus (SLE) may impact multiple organs and systems (Lee & Amengual, 2020). Furthermore, SLE is classified as a highly heterogeneous autoimmune illness, which means that its symptoms and severity can vary greatly between individuals. This occurs because SLE can impact almost every organ system in the body (Ocampo-Piraquive et al., 2018). Chronic discoid lupus, for example, is frequently the earliest symptom of SLE in patients, accounting for about 10% of all SLE cases. About 5-10% of people with discoid lupus will develop SLE (Dipiro et al., 2021). An estimated 5.14 cases of SLE are reported for per 100,000 people worldwide each year, with a greater frequency in women. SLE affects around 8.82 out of every 100,000 women and 1.53 out of every 100,000 men per year (Tian et al., 2023). Given the complex pathophysiology of SLE and the variability in patient responses to conventional treatments, there is an urgent need to systematically review targeted therapies such as rituximab to consolidate current evidence, clarify mechanisms of action, and improve clinical management.

Rituximab (RTU) is a monoclonal antibody that is chimeric against CD20. Monoclonal RTU anti-CD20 has demonstrated efficacy in treating autoimmune diseases like SLE by depleting β cells (Cambridge et al., 2014; Pirone et al., 2017; Robinson et al., 2022). RTU acts by using the patient's immune system to kill β cells, mostly through antibody-dependent cellular cytotoxicity, which depletes β cells (Leandro & Isenberg, 2021). Thus, this review's objective is to elucidate the mechanism of action of RTU as a therapeutic agent targeting β cells in patients with SLE.

METHODS

A literature review methodology was used in writing this paper. From January 2024 to March 2024, the search for articles in the literature was limited to the years 2013–2023. The Embase database was used for electronic literature searches. In line with the article's theme, "Mechanisms and Targeted Therapy of Rituximab in Systemic Lupus Erythematosus," the authors used Boolean keywords combined with AND/OR as keyword combinations. "MECHANISM," AND "TARGETED THERAPY," AND "RITUXIMAB" OR "MONOCLONAL ANTIBODY," AND "SYSTEMIC LUPUS ERYTHEMATOSUS," AND "Beta Cells" were the selected keywords. A total of 1,002 journals were obtained from the Embase database literature search, but in this literature review, based on inclusion criteria, only journals focusing on adult patients over 18 years of age with a diagnosis of SLE and pharmacological therapy, particularly immunosuppressive and biological therapies, were included. Meanwhile, literature from opinions and abstracts without complete text, non-SLE patients, or other autoimmune conditions was excluded. Seven journals underwent final evaluation based on inclusion and exclusion criteria.

RESULT AND DISCUSSION

Lymphoma

In order to treat lymphoma patients, monoclonal antibodies that target β cells were initially developed. The WHO classifies the primary differences in lymphoma based on the cell of origin, which includes T cells, β cells, and natural killer (NK) cells. With an average age of 63 years, the incidence of lymphoma in the United States was approximately 22 per 100,000 between 2009 and 2013 (Matasar & Zelenetz, 2008). Ten percent of lymphomas are Hodgkin lymphoma (HL), while ninety percent are non-Hodgkin lymphoma (NHL). Determining whether the incidence of lymphoma is classified as high or low is crucial from a clinical standpoint. NHL is divided into β-cell, T-cell, and natural killer cell kinds, whereas HL is divided into classical and non-classical varieties (Mugnaini & Ghosh, 2016). NHL is also more common in the United States, where diffuse large β-cell lymphoma (DLBCL), aggressive β-cell lymphoma, or follicular lymphoma (FL), which are classified as indolent β-cell lymphoma (IBCL), account for over half of newly diagnosed NHL cases. Mantle Cell Lymphoma (MCL), Burkitt Lymphoma (BL), Peripheral T-Cell Lymphoma (PTCL), Small Lymphocytic Lymphoma (SLL), and Marginal Zone β-Cell Lymphoma (MZL) are additional NHL subtypes (Matasar & Zelenetz, 2008).

Monoclonal antibodies that target β cells are used as treatment of lymphomas, including Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Membrane-bound antibodies are expressed by all mature β cells. The β-cell receptor (BCR) is formed by immunoglobulin (Ig) joining forces with molecules and cofactors. V(D)J recombination-induced changes to the Ig gene are essential for producing of healthy β cells. Furthermore, somatic hypermutation and Ig gene class switching play a crucial role in the antigen-induced differentiation of β cells. On the other hand, β-cell lymphoma may arise if these mechanisms fail. This can lead to β-cell cancers, which are defined by proto-oncogenes moving to Ig loci. The expression of the β-cell antigen receptor is necessary for several β-cell lymphomas. Because of the high rate of cell proliferation and mutagenesis processes, germinal center β cells are likely to be the source of β-cell malignancies (Kuppers & Walker, 2013).

Systemic Lupus Erythematosus (SLE)

Hematological symptoms such as hemolytic anemia, leukopenia, and thrombocytopenia are common in systemic lupus erythematosus (SLE), a systemic autoimmune disease (Cambridge et al., 2014). Clinically, SLE can cause a variety of symptoms, ranging from minor to severe. The

degree of major organ involvement determines the prognosis for SLE, which is uncertain (Lee & Amengual, 2020). Although it is still unknown how β cells contribute to the development of SLE, the disease is characterized by persistent β-cell hyperactivity. However, β cells are essential for the pathophysiology of SLE and for preserving an environment of chronic inflammation (Parodis et al., 2022). Poor immune regulatory mechanisms, including apoptotic cell and immune complex clearance, are also linked to SLE and play a major role in the disease's course (Lee & Amengual, 2020; Mak & Kow, 2014). Serum levels of interferon (IFN), a protein involved in the body's immune system, are elevated in patients with autoimmune diseases such as SLE. Peripheral tolerance is weakened by enhanced type I IFN bioavailability, which stimulates immature myeloid dendritic cells (mDCs). Overall, by stimulating autoreactive T cells and β cells, which in turn generate autoantibodies, mDCs and IFN play a crucial part in triggering maladaptive immune responses in SLE (Banchereau & Pascual, 2006). One of the effector cell types in charge of maintaining the inflammatory response is autoreactive B cells (Lee & Amengual, 2020).

Patients with SLE have tissue damage and inflammation due to autoantibodies complexed with nucleic acids. As immunomodulators, lupus autoantibodies trigger the production of inflammatory mediators and type I IFN. An important part of this process is the differentiation of β cells into cells that produce autoantibodies (Crow, 2023). SLE is characterized by the generation of autoantibodies that target proteins linked with nucleic acids, especially double-stranded DNA. The use of treatments that target β cells, like rituximab, is supported by this feature (Basta et al., 2020; Ehrenstein & Shipa, 2023; Galanopoulos et al., 2017). Additionally, this process explains the disease's complicated and varied symptoms in SLE patients. Fatigue, sadness, anxiety, headaches, joint pain, nausea, and/or stomach pain are common symptoms of SLE. Fever, kidney failure, pleural effusion, hypertension, anemia, thrombocytopenia, lymphadenopathy, and Raynaud's phenomenon are among the clinical manifestations of SLE (Dipiro et al., 2021).

Rituximab

Rituximab, also known as MabThera or Rituxan, is a chimeric monoclonal antibody that targets human CD20, a non-glycosylated phosphoprotein that is found on the surface of the majority of healthy and malignant β cells. Autoantibodies are typically produced when pathogenic T cells activate β cells (Levitsky et al., 2013). In order to control cell cycle activity and differentiation, CD20, an essential membrane protein, is produced when pro-β cells differentiate into plasma cells. Patients who lack CD20 have independent T-cell immunodeficiency, according to in vitro research (Alamilla Sanchez et al., 2021; Beckwith & Lightstone, 2014).

Rituximab (RTU) treatment is an unconjugated chimeric monoclonal antibody with a molecular weight of 145 kD that is made up of two heavy chains, each of which is 451 amino acids long, and two light chains, each of which is 213 amino acids long. Its half-life is roughly 174 hours (ranging from 26 to 422) following the fourth injection and 59.8 hours (ranging from 11.1 to 104.6 hours) following the first. In patients with kidney impairment, the half-life rises to 10–14 days (Alamilla Sanchez et al., 2021). Only hemodialysis can eliminate RTU monoclonal antibodies, which can stay in the bloodstream for three to six months (Alamilla Sanchez et al., 2021; Beckwith & Lightstone, 2014). Headache, nausea, urticaria, and hypertension/hypotension are typical adverse effects during the initial infusion. However, premedication with glucocorticoids can help moderate these symptoms (Alamilla Sanchez et al., 2021).

Randomized controlled trials (RCTs) have not shown that rituximab (RTU) is effective in SLE, despite several case reports and open-label clinical trials suggesting that it has positive effects. Patients with external involvement were treated with RTU in conjunction with immunosuppressive medications as part of the EXPLORER clinical trial, which assessed the safety and effectiveness of RTU in patients with moderate to severe active SLE. LUNAR, another clinical trial, evaluated lupus nephritis by examining the use of RTU in individuals with the disease in conjunction with corticosteroids and mycophenolate mofetil. Perhaps as a result of the

trials' brief duration or the endpoints selected, neither study demonstrated any appreciable advantages.

When paired with cyclophosphamide instead of mycophenolate mofetil, RTU may be more beneficial for African American and Hispanic patients with lupus nephritis than for patients of other races, according to analyses from prior clinical trials. Within two years of randomization, 69% of the 144 participants in the LUNAR study received a lupus nephritis diagnosis, with half of them having early-stage lupus nephritis. The RTU and placebo groups did not vary statistically in their renal response rates (CRR, renal response, or no response) at week 52 (P = 0.55). A predetermined subgroup analysis of overall renal responses, however, showed that Black patients treated with RTU had a greater response rate than those in the placebo group at week 52 (70% vs 45%), similar to the EXPLORER experiment. Furthermore, RTU demonstrated a decrease in the UPC at week 52, and by week 78, there was a statistically significant difference between the two groups (P = 0.04). RTU is therefore still a viable treatment option for severe hematological lupus and refractory lupus nephritis (Beckwith & Lightstone, 2014; Dipiro et al., 2021; Levitsky et al., 2013; Wiesik-Szewczyk & Olesinska, 2012).

Mechanism of Rituximab

The monoclonal antibody rituximab (RTU) is known to target β cells and bind to CD20 selectively. RTU therapy was first utilized to treat lymphoma patients by binding to CD20, which is expressed on normal β cells and almost all β-cell lymphomas. Through a variety of mechanisms, including Antibody-Dependent Cellular Cytotoxicity (ADCC), Complement-Dependent Cytolysis (CDC), complement-dependent cellular cytotoxicity, and direct apoptosis induction through CD20 engagement by RTU CD20 binding takes place **Figure 1**. RTU-induced death of malignant β cells probably promotes the development of lymphoma-specific T lymphocytes and the cross-presentation of lymphoma antigens by antigen-presenting cells (APCs) (Bello & Sotomayor, 2007; Salles et al., 2017; Weiner, 2010).

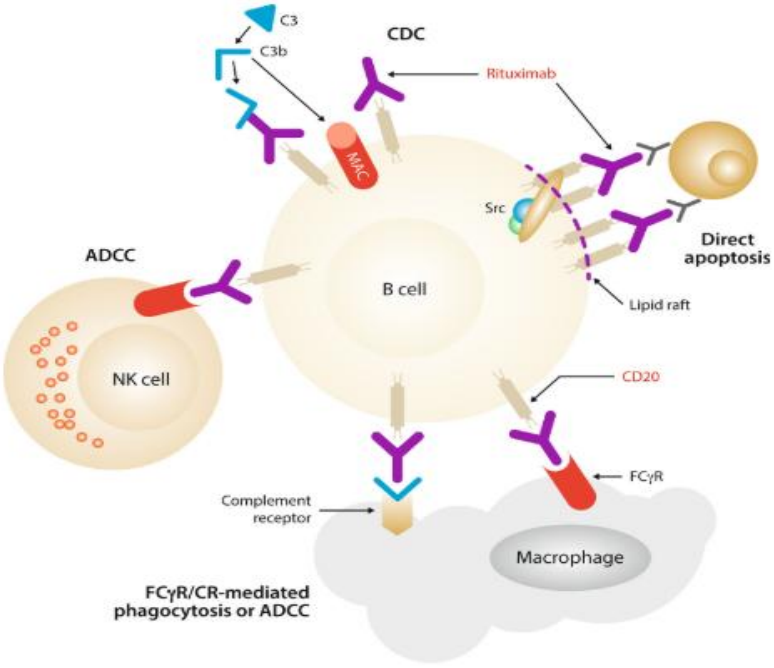

Figure 1. Mechanism of Rituximab (RTU) in Lymphoma (Salles et al., 2017)

Rituximab (RTU) is a treatment for lymphoma patients; however, it can also be used as an alternate treatment for SLE. The generation of autoantibodies in SLE contributes to the creation of an inflammatory response via a number of pathways, such as the stimulation of innate immune cells to create cytokines and interferons. Targeting β cells is therefore one

way to treat SLE (Athanassiou & Athanassiou, 2023). The pathophysiology of SLE primarily involves the dysregulation of B lymphocytes, with β cells acting as antigen-presenting cells that expose T cells to autoantigens. Cytokines are produced and activated by T cells. T cells and β cells both stimulate one another, and β cells produce autoantigens that cause autoantibodies to be produced (Wu et al., 2020).

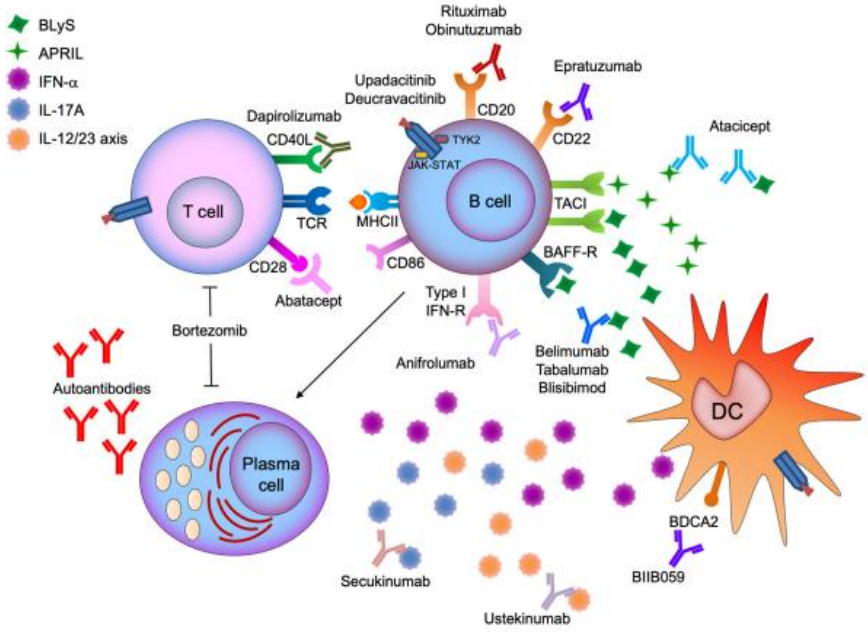

Figure 2. Mechanism Action of Rituximab Targeting β Cells (Parodis et al., 2022)

Rituximab (RTU) reduces the amount of β cells by depleting β cells, which is how it treats SLE. Since progenitor and plasma cells do not express the CD20 molecule, Rituximab only affects CD20-positive β cells, leaving the progenitor and plasma cells unaffected **Figure 2** (Athanassiou & Athanassiou, 2023; Sanz, 2016). Rituximab destroys β cells by complement-mediated and antibody-dependent cytotoxicity. Additionally, by causing β cell apoptosis and inhibiting proliferation, rituximab can be used in refractory SLE with renal and neuropsychiatric symptoms. Rituximab is an excellent treatment for SLE that has been used for more than a decade. It lowers immunological markers and disease activity while also helping to lower steroid dosages (Moroni et al., 2014; Witt et al., 2013). Additionally, rituximab has proven helpful for SLE patients who have cutaneous, hematologic, and renal symptoms. Apart from its mechanism of β cell depletion, it also has an effect on β cells and macrophages by binding to the Fc gamma receptor IIB, which can prevent their activation (Basta et al., 2020).

Rituximab Cell Targets

RTU treatment uses CD20 to target B cells in lymphoma. B lymphocytes have a unique cell surface protein called CD20 (Eisenberg & Looney, 2005). The majority of lymphoma types in non-Hodgkin lymphoma (NHL) exhibit the CD20 immunophenotype, according to the characteristics of lymphoma; however, this is not the case for Hodgkin lymphoma (HL) (Matasar & Zelenetz, 2008). Additionally, RTU targets β cells, making it an alternate therapy for immunological illnesses like SLE. In addition to generating autoantibodies, β cells also control other cell types, release cytokines, and present antigens, all of which contribute to the immunopathogenesis of autoimmune disorders (Eisenberg & Looney, 2005). RTU in SLE targets the CD20-specific β cell surface, just like it does in lymphoma (Basta et al., 2020) **Table 1**.

Several studies, such as those by An et al. (2019) and Rosenzwajg et al. (2017), reported that RTU therapy for SLE patients targets β cells by depleting and reducing β cell numbers (An et al., 2019; Rosenzwajg et al., 2017). The targeting

of β cells in RTU therapy for SLE is further explained by more recent research (Galanopoulos et al., 2017; Pirone et al., 2017). More precise information is provided by the most recent study, which confirms that RTU treatment for SLE depletes β cells by targeting them with CD20, a β cell-specific cell surface molecule (Athanassiou & Athanassiou, 2023; Basta et al., 2020).

Table 1. Mechanism and Cells Target of Rituximab (An et al., 2019; Athanassiou & Athanassiou, 2023; Basta et al., 2020; Galanopoulos et al., 2017; Jordan & D'Cruz, 2016; Pirone et al., 2017; Rosenzwajg et al., 2017)

Authors	Year	Mechanism of Rituximab	Rituximab Cells Target
Athanassiou *et al*	2023	Rituximab works as a monoclonal antibody targeting β cell depletion with anti-CD20.	β Cells
Basta *et al*	2020	Rituximab works as a chimeric monoclonal antibody that selectively targets the specific surface molecule CD20 on β cells.	β Cells
An *et al*	2019	Rituximab counteracts the effects of anti-CD20 therapy by increasing β cell depletion, thereby boosting the production of β lymphocyte stimulators, which promote B cell recovery and autoreactive β cell generation.	β Cells
Rosenzwajg *et al*	2017	Rituximab can cause β lymphocytes to thin or shrink. An early indicator of rituximab response could be a rise in the proportion of Treg cells.	β Cells
Galanopoulos *et al*	2017	Polyclonal β cell hyperreactivity has been linked to SLE. A chimeric monoclonal antibody called rituximab depletes β cells by attaching itself to the CD20 antigen on the surface of β lymphocytes.	β Cells and Treg Cells
Pirone *et al*	2017	Rituximab works as a monoclonal antibody targeting β cell depletion with anti-CD20.	β Cells
Jordan and D'Cruz	2016	Rituximab is a chimeric monoclonal antibody that uses the CD20 surface marker to specifically target β cells. Although rituximab may have other effects by binding to the gamma Fc IIB receptor on β cells and macrophages and preventing their activation, it is unclear if this mechanism of action is limited to β cell depletion.	β Cells

CONCLUSIONS

A chimeric monoclonal antibody called Rituximab (RTU) is specific for CD20, a non-glycosylated phosphoprotein found on the surface of β cells. RTU can be utilized as an alternative treatment for SLE in addition to being used as a treatment for lymphoma with a mechanism of action that depletes, inhibits, and targets the activation of β cells by binding to the Fc gamma IIβ receptor on both β cells and macrophages. Numerous studies have demonstrated that RTU can be utilized to treat lymphoma as well as SLE because of its shared therapeutic target in both conditions.

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AUTHORS' CONTRIBUTIONS

The study's concept, methodology, literature search, and analysis were all created by Afifah Listiadewi. Suharjono helped with the article's revision. Every author took part in the manuscript's evaluation and finalization.

CONFLICT OF INTERESTS

With regard to this publication, the writers have no conflicts of interest.

ETHICAL CONSIDERATION

Plagiarism, data manipulation, multiple publication, and other ethical difficulties have all been fully observed by the author.

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