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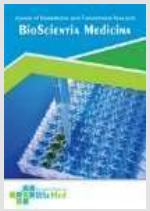

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The Role of Rituximab in the Management of Heart Failure

Rizki Bastari[1*], Taufiq Indrajaya[2], Syamsu Indra[2]

[1]Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

[2]Division of Cardiovascular, Department of Internal Medicine, Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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***Corresponding author:**
Rizki Bastari

E-mail address:
ribasrizki@gmail.com

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A B S T R A C T

Rituximab is a chimeric monoclonal antibody mice/humans that bind the transmembrane antigen, CD20 specifically. The mechanism of heart failure is mediated by neurohormonal pathways: the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and the natriuretic peptide system, thereby triggering activation of the immune system. This literature review will discuss the role of B cell targeted therapy, in this case rituximab in the management of heart failure. Modulation of the immune response holds great promise in the 30% of cases of myocarditis where inflammation does not resolve and progression to chronic inflammatory dilated cardiomyopathy occurs. Pharmacologically, rituximab is a monoclonal immunoglobulin G1 antibody drug that is given intravenously. Rituximab targets the CD20 antigen expressed on the surface of mature B lymphocytes, including memory B cells but not on stem cells or plasma cells. In conclusion, rituximab causes a selective and temporary decrease in the CD20+ B cell subpopulation and represents a more specific and targeted approach to B cell-induced disorders including heart failure.

1. Introduction

Heart failure is a clinical syndrome characterized by shortness of breath and fatigue caused by abnormalities in the structure or function of the heart.[1] Based on 2018 Basic Health Research data, the prevalence of congestive heart failure in Indonesia is 1.5% or around 1,017,290 people.[2] The mechanism of heart failure is mediated by neurohormonal pathways: the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, and the natriuretic peptide system, thereby triggering activation of the immune system.[3] This mechanism increases inflammation and inflammation causes heart failure. The immune system plays a central role in the progression of heart failure.[4]

Recent research shows that cells of the body's immune system not only contribute to pathology but are also key regulators of heart function.[5] Currently, there are no pharmacological interventions introduced in clinical guidelines to treat heart failure by modulating the immune system that provides additional clinical benefit.[6] Understanding the pathogenesis related to B cell activation is very important as a basis for the management of heart failure.[7] This literature review will discuss the role of B cell targeted therapy, in this case rituximab in the management of heart failure.

Rituximab profile

Rituximab is a chimeric monoclonal antibody in mice/humans that binds the transmembrane antigen,

CD20 specifically. This antigen is located on pre-B lymphocytes or mature B lymphocytes but is not present on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues. This antigen is expressed on >95% of all non-Hodgkin's lymphoma (NHL) B cells. Rituximab binds to the CD20 antigen on B lymphocytes and initiates an immunological reaction that mediates B cell lysis.[8,9] Rituximab works by binding to the transmembrane surface antigen CD20 expressed on B cells (Figure 1). The most common side effect due to the use of rituximab is infection. Other side effects that may arise are infusion reactions, anaphylactic reactions, and decreased levels of immunoglobulin (Ig) G and Ig M. Fatal but rare events are progressive multifocal encephalopathy, prolonged neutropenia, and fatal viral reactivation.[9,10]

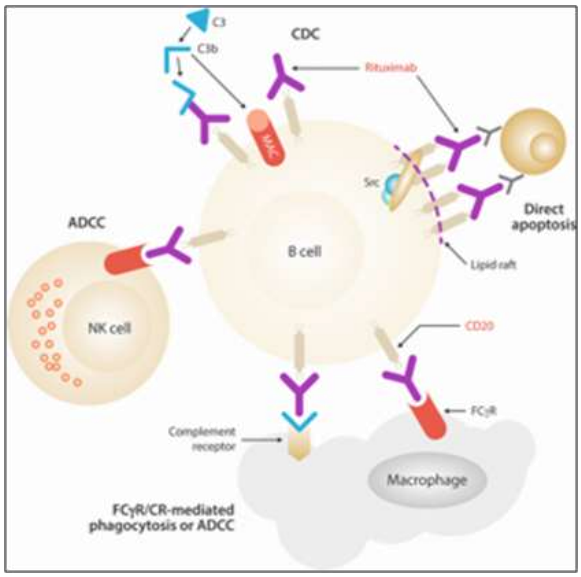

Figure 1. Mechanism of rituximab-mediated B cell death.[9,10]

Rituximab pharmacology

Pharmacologically, rituximab is a monoclonal immunoglobulin G1 antibody drug that is given intravenously. This drug was developed for the treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, granulomatosis with polyangiitis, rheumatoid arthritis, and microscopic polyangiitis (GMA). The target of rituximab is the CD20 protein which is expressed on the surface of most B cells. Rituximab is a chimeric antibody that combines parts of mice and man.[8] Rituximab causes a decrease in the number of B cells by (1) Fc receptor gamma-mediated, antibody-dependent cytotoxicity and phagocytosis; (2) complement-mediated cell lysis; (3) growth arrest, and (4) B cell apoptosis.[8]

Rituximab is known to have a long elimination half-life, approximately 3 weeks. The distribution and elimination of rituximab will be influenced by the binding between antibodies and antigens. Rituximab has a different onset and duration of action depending on the patient's medical condition. The onset if given for non-Hodgkin's lymphoma is around 3 weeks, while for rheumatoid arthritis it is 2 weeks. The duration of action of B cell depletion is around 6-9 months in non-Hodgkin's lymphoma, while in rheumatoid arthritis it is 6 months. Rituximab can pass through the placenta and breast milk, although at small levels.[11]

The role of rituximab in the management of heart failure

Inflammation has been considered as a potential treatment target in the search for new therapies for heart failure especially those with low ejection fraction.[11] Myocardial damage and tissue

hypoperfusion can induce cytokine production which can increase the development of cardiac dysfunction. Nonetheless, clinical trials on inhibitors of tumor necrosis factor-α (TNFα) or interleukin-1β (IL-1β) have shown good results. This may be due to the fact that activation of inflammatory pathways is limited and inflammation is not an important disease determinant in most patients.[10,11]

Modulation of the immune response holds great promise in 30% of cases of myocarditis where inflammation does not resolve and progression to chronic inflammatory dilated cardiomyopathy occurs. A total of 42% of patients showed myocardial inflammation on endomyocardial biopsy (EMB) among 202 dilated cardiomyopathy patients. (DCM) from ≥6 months of age. Patients assigned to steroids and azathioprine were randomized to decrease left ventricular (LV) volume, recovery of function, and improvement in NYHA class during the first 3 months of treatment. This effect persisted for 2 years, although there was no difference in survival. Another study evaluated 85 patients with DCM who were randomized to prednisone and azathioprine or placebo for 6 months. They showed the positive effect of immunosuppression therapy on cardiac remodeling, where the mean LVEF increased from 26% to 46%, symptoms of heart failure also improved, and no major side effects were found.[12] However, both steroids and azathioprine have a wide spectrum of activity and a poor safety profile, prompting the search for more selective therapeutic approaches. Antibody-dependent mechanisms contributing to cardiac injury primarily include the direct effect of anti-cardiac antibodies and subsequent activation of the complement system (Figure 2).

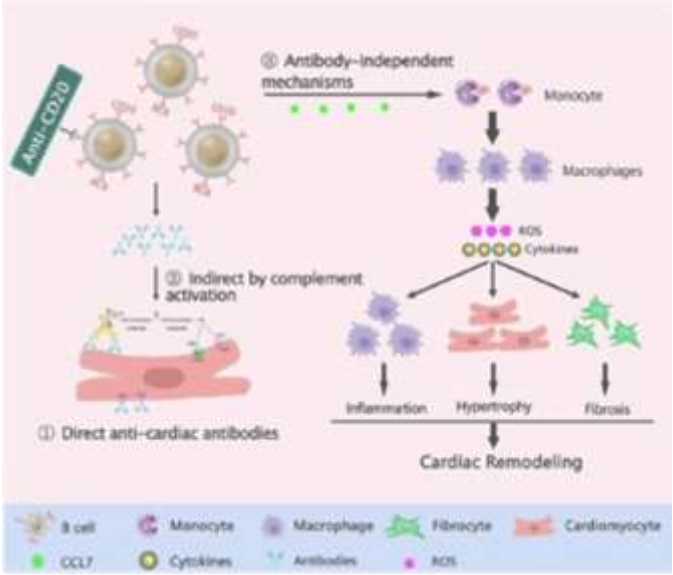

Figure 2. Potential mechanisms of B cell participation in cardiac remodeling and heart failure.

Direct anti-cardiac antibodies

In animal models, antibodies to certain cardiac proteins have also been shown to cause cardiomyopathy. Antibodies to troponin I were found to produce dilated cardiomyopathy in PD-1-deficient mice. Another cohort study identified anti-desmoglein-2 (Anti-DSG2 Antibody) as a sensitive and specific biomarker for arrhythmogenic right ventricular cardiomyopathy (ARVC). In humans, anti-DSG2 antibody levels correlate with the burden of premature ventricular contractions; In vitro, antibodies cause gap junction dysfunction, a common feature of ARVC.[13]

Histological analysis of human myocardial tissue with end-stage heart failure revealed immunoglobulin G (IgG) deposition. in 70% of heart tissue samples.[12] Analysis of nearly 50% of biopsies showed IgG3

positive, with a smaller proportion of C3c deposits staining positive. The presence of IgG3 and C3c in the myocardium has been shown to correlate with the duration and severity of heart failure. Moreover, both left ventricular diastolic dysfunction and end-stage HFrEF patients showed increased levels of IgG1 and IgG3, indicating the presence of an antibody-mediated immune response in cardiac remodeling.[13]

Effect of complement on myocardial injury

The complement system is an important component of the innate immune response and can be activated through three pathways during heart failure. The classical pathway is initially activated by IgM or IgG antigen/antibody complexes and induces the formation of a membrane attack complex (MAC) through a series of reaction cascades. The alternative pathway of the complement system is activated through direct binding of bacteria and fungi independent of antibody interactions. The lectin pathway is a new pathway that activates the complement system. The molecule that initiates this pathway is collectin (mannose- and ficolin-binding lectin), which is a complex multimeric lectin.[12]

Complement C5a can induce cardiac hypertrophy and perivascular fibrosis which causes remodeling of the heart muscle. C5a is also effective as a chemokine for inflammatory mediators by modulating the TGF-β/Smad2/3 pathway in the heart. C5b-9 induces tumor necrosis factor-α expression (TNF-α) in cardiomyocytes and contributes to cardiomyocyte hypertrophy, fibrosis, and apoptosis. This process is an important component of injury in heart failure.[12]

Antibody-independent mechanisms cause cardiac injury

In addition to acting through antibodies and complement, activated B cells can secrete cytokines and chemokines to directly modulate cardiac function and induce cardiac remodeling. B cells have been shown to be directly involved in cardiac remodeling through regulation of the cytokines TGF-β and IL-6, and are responsible for maintaining an adverse inflammatory environment through the production of TNF-α, IL-1β and IL-6. TNF-α-secreting B cells in DCM patients were associated with increased cardiac fibrosis, as confirmed by late gadolinium enhancement on cardiac MRI and increased serum pro-collagen type III levels.[14] B cells also exert biological effects by altering cardiac function through the secretion of chemokines. A recent study reported mature B lymphocytes selectively produce the chemokine CCL7, which can induce the mobilization and recruitment of Ly6Chi monocytes to the heart, causing tissue injury and impaired myocardial function in a mouse model.[15]

Rituximab targets the CD20 antigen expressed on the surface of mature B lymphocytes, including memory B cells but not on stem cells or plasma cells. Rituximab causes a selective and transient decrease in the CD20+ B cell subpopulation and represents a more specific and targeted approach to B cell-induced disorders. B lymphocytes influence and regulate the immune response through several mechanisms and are an important link between the innate and adaptive immune systems.[9,15]

Reports the results of the first clinical experience using rituximab in six DCM patients. Six patients were evaluated, patients had systolic dysfunction (LVEF ranging from 14-45%) for several months (in two cases) and about five years (in four other cases), CD20+ >7 cells/mm^2, and there was no evidence of viral genomes in EMB. Two of them were treated with steroids and azathioprine. The patient received two doses of rituximab (375 mg/m^2 each, 4 weeks apart, and together with cortisone 150 mg to avoid infusion reactions coupled with standard heart failure therapy.[9] This study shows that exposure to rituximab is much lower than for treatment of hematological disorders or vasculitis (375 mg/m^2 weekly for up to 8 weeks) or rheumatoid arthritis (1000 mg/m^2 given twice for 2 weeks). This study showed that rituximab was well tolerated by six patients, except for one patient who had a long history of disease and had previously undergone immunosuppressive therapy. All patients demonstrated a response to rituximab, with significant improvements in LVEF, LV end-diastolic diameter, NYHA class, or N-terminal pro-B-natriuretic peptide.[9]

Two patients with shorter disease histories (Patients 1 and 2) showed the greatest response to rituximab. Interestingly, this patient also had the highest number of CD20+ cells on initial EMB (20.25 and 633 cells/mm^2, respectively), and CD20+ cells were not detected on EMB during follow-up. In contrast, CD20+ cells in patients with a longer history of disease tend to be lower (one of which is 10 cells/mm^2) and did not respond to rituximab, the patient also showed an increase in the number of CD20+ cells after biopsy (17.5 cells/mm^2). This suggests that rituximab may be considered in patients with DCM when EMB shows significant CD20+ cell infiltration (>7 cells/mm^2) and there is no evidence of viral infection, especially when the onset of heart failure symptoms is recent.[10]

The phase II clinical trial conducted by Trujillo et al evaluated the safety of rituximab dosing in patients with class III/IV functional heart failure according to the NYHA classification with reduced EF and who do not respond adequately to standard treatment. Inadequate response to treatment was defined as multiple hospitalizations and worsening of cardiac functional class with optimal compliance and dose of standard treatment. Patients eligible for HFrEF had to be based on EF≤40% by echocardiography or cardiac MRI technique, aged 40–60 years and diagnosed <12 months previously enrolled in the study. This study is currently ongoing and has not yet been completed.[16]

Another study proved that heart biopsies in 100 patients experiencing end-stage heart failure and 40 donor patients showed increased levels of IgG with cardiac antigen. 71% of these patients had an increase in IgG, 48% of which were the IgG3 subtype. The proportion of patients with ischemic heart disease who showed an increase in IgG levels was 65%, while in patients with non-ischemic etiology, the increase in IgG levels was 76%. As many as 31% of all samples showed activation of the complement system. This study also shows the presence of anticardiac antibody deposits in the form of ATP synthase B-subunit which are abundant in the sarcolemma, which indicates antibodies that resemble anticardiac antibodies. This is also confirmed by the discovery of Ig3 and C3c deposits distributed in the same sarcolemma. Activation of the immune system is a late event in heart failure identified by the high proportion of IgG3 and C3c deposits in patients who suffer from the disease longer. These data support the suspicion of a role for B lymphocytes that release special proteins to the heart in the pathogenesis of heart failure. B cells are the primary mediators of injury found in patients with dilated cardiomyopathy, where elimination of these specific antibodies can significantly improve heart conditions.[15] In mice, administration of anti-CD20 showed improvements in heart function in mice with heart failure, wherein in these mice a reduction in fibrosis was found, a reduction in ventricular dilatation, the result of which was an improvement in ejection fraction.[7]

2. Conclusion

Rituximab targets the CD20 antigen expressed on the surface of mature B lymphocytes, including memory B cells but not on stem cells or plasma cells. Rituximab causes a selective and transient decrease in the CD20+ B cell subpopulation and represents a more specific and targeted approach to B cell-driven disorders including heart failure.

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