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BIOMEDICAL SCIENCES

Exploring the Potential Role of C1-Esterase Inhibitor in Preventing Heart Transplant Graft Rejection

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Abstract

Heart transplantation is considered the standard therapy for patients with end-stage heart failure who do not respond to treatment with drugs or devices. Dr. Christian Barnard performed the first heart transplant surgery in South Africa in December 1967. Since then, significant advancements have been made in the use of immunosuppressive drugs and monitoring techniques to detect and prevent post-transplant complications, leading to improved patient survival after surgery. This article discusses the potential of C1 esterase inhibitors in preventing heart transplant rejection and improving survival for end-stage heart failure patients.

Keywords: C1 esterase inhibitor; heart transplantation; outcomes; complications.

Introduction

Cardiovascular disease is the leading cause of death globally, with death rates ranging from 73.6 to 432.2 per 100,000 people per year [1]. Heart failure, the final outcome of various cardiovascular diseases, affects more than 26 million patients worldwide [2]. Despite advancements in heart failure treatments, such as new drugs (SGLT2i) and mechanical support, the mortality rate remains high at 68.7 per 100,000 people [3]. According to the 2022 American Heart Association recommendations on the diagnosis and treatment of heart failure in adults, heart transplantation is recommended for patients with stage D heart failure that is refractory to optimal medical therapy [4]. Heart transplantation can significantly improve patient survival, increasing life expectancy from less than 2 years to more than 12 years [5, 6]. However, for organ transplant patients, particularly heart transplant recipients, one of the most significant challenges is graft rejection. Risk factors for graft rejection include hypercholesterolemia, coronary artery disease, young recipient age, and insulin resistance.

Overview of complications related to graft rejection in organ transplantation

Graft rejection can be classified as hyperacute rejection, acute rejection, antibody-mediated rejection, and chronic rejection. Each type of rejection has its own timeline and classification, with distinct pathophysiological mechanisms. However, they all involve the immune response, in which inflammatory pathways, inflammatory cells such as T and B cells, and the complement system play crucial roles.

Hyperacute rejection

Hyperacute rejection is the most severe form of graft rejection. This reaction occurs when high concentrations of preformed antibodies against the donor's Major Histocompatibility Complex (MHC) antigens cause severe rejection [7]. Complement-dependent graft rejection can happen within minutes or hours after reperfusion. Antibodies bind to antigens on graft endothelial cells, triggering complement-mediated lysis, endothelial damage, and coagulation pathways, leading to immediate graft thrombosis and organ failure. Although it cannot be cured, alloantibody-related hype rejection can be almost entirely prevented by performing immunological cross-matching to detect

donor-specific antibodies.

Acute rejection

If post-transplant immunosuppression is insufficient, the recipient's body may reject the graft. This rejection, mediated by T-cells, can occur as early as a few days and typically within six months after the organ transplantation. This acute rejection is triggered by the recipient's immune system recognizing the donor's Major Histocompatibility Complex (MHC) as foreign. Pathologically, acute graft rejection is characterized by inflammatory reactions and infiltration of interstitial cells with or without blood vessels by lymphocytes.

Antibody-mediated rejection

Antibody-mediated Rejection (AMR), also known as humoral rejection, primarily involves the production of specific antibodies by Memory B cells, which are generated with the help of helper T cells. In addition, antigen-presenting T cells are activated post-transplantation to produce these specific antibodies. Clinically and pathologically, distinguishing between T-cell-mediated rejection and AMR can be challenging and relies heavily on specific pathology results. AMR is characterized by the accumulation of neutrophils and mononuclear cells, small vessel thrombosis, and often the deposition of the complement component C4d. The presence of C4d is linked to leukocyte deposition, fibrin necrosis, and the circulation of donor-specific antibodies (DSA). Both clinical and pathological evidence points to the activation of the complement system, particularly through the classical pathway, as a crucial factor in AMR. This pathway enhances the damage induced by antibodies, leading to disease progression. Furthermore, the interaction between DSA and the C1q component of complement, resulting in increased C4d deposition, is a significant predictor of graft rejection. The extent of C4d deposition in the graft is a critical factor in both acute and chronic AMR stages. It is widely agreed among researchers that high levels of DSA that bind complement following transplantation are associated with poorer outcomes.

Chronic rejection

This complication usually occurs 6 months to several years after implant surgery. The pathogenesis involves a combination of both humoral and cellular immunity, where the donor's MHC class II antigens interact with the recipient's CD4 T cells. This interaction leads to the differentiation of these cells into helper T cells that induce inflammation in both the parenchyma and endothelium, similar to acute rejection. Chronic rejection in heart transplants often manifests as cardiac allograft vasculopathy (CAV). According to 2013 data, CAV was observed in approximately 8% of patients in the first year, 30% within five years, and 50% within ten years post-transplantation [8]. The complement system, particularly through C4d deposition linked to circulating donor-specific antibodies (DSA), plays a crucial role in delayed graft dysfunction. These immune responses are comparable to those causing severe obstructive bronchiolitis in lung transplants, where the average survival time decreases from 5.2 years to 1.5 years, a scenario also noted in heart transplant cases. Furthermore, the deposition of C4d and/or C3d along with DSA positivity in the graft increases the risk of coronary artery complications and graft dysfunction [9].

The complement system and its role in the immune system

The complement system is a crucial component of the body's immune regulation, playing a multifaceted role in the immune response. It serves not only to activate the inflammatory system but also regulates, detects, and enhances the activity of various immune cells, including macrophages and T cells (Figure 1). The complement system operates through three main pathways:

The classical pathway

The classical pathway of the complement system is initiated by the protein complex C1, which is composed of three subunits: C1q, C1r, and C1s. The activation process begins when C1q binds to the Fc fragments of the IgG or IgM heavy chains—a recognition step critical for pathway initiation. Upon binding, C1q activates C1r, which in turn functions as a protease to activate C1s. Once activated, C1s acts as a protease that cleaves proteins C4 and C2. C4 is split into two fragments: C4a, which acts as an anaphylactic toxin and participates in the inflammatory response, and C4b, which binds either to the antigen-antibody complex or directly to a cell surface where antibodies are attached. This binding is essential for the continuation of the classical pathway. The activated C1s also cleaves C2 into two fragments: C2b, which is soluble, and C2a. The C2a fragment combines with C4b to form the C4b2a complex, functioning as a C3 convertase. The C3 convertase cleaves C3 into C3a, which is involved in the inflammatory response, and C3b, which attaches to cell surfaces or antibodies, initiating further complement activation. This leads to the formation of the C4b2a3b complex, which functions as the C5 convertase. Additionally, C3b binds to receptors on the surfaces of pathogen proteins or antibodies, participating in the formation of immune complexes.

The alternative pathway

In the alternative pathway of the complement system, the central component C3 is cleaved into two fragments: C3a and C3b. C3b binds to factor B in the plasma, which is then cleaved by factor D into two fragments: Ba and Bb. The Bb fragment combines with another C3b molecule to form the complex C3bBb, known as the C3 convertase of the alternative pathway. This convertase cleaves additional C3 molecules, generating further C3a and C3b fragments. Some of the C3b molecules bind to the existing C3bBb complex, forming the (C3b)2Bb complex, which acts as the C5

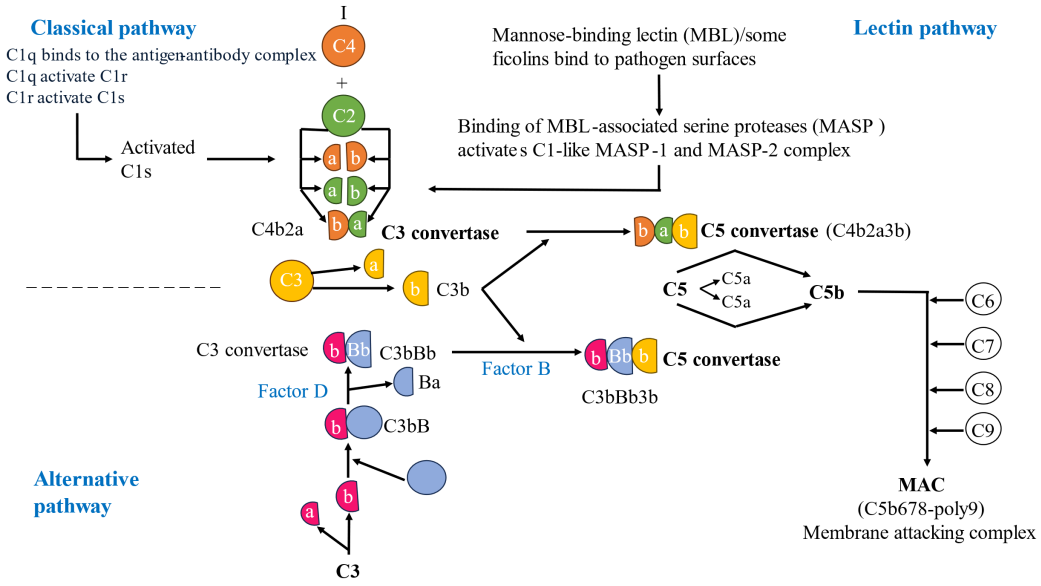

Figure 1: The complement activation pathways. The complement system is activated through three primary pathways: the classical pathway, the lectin pathway, and the alternative pathway. Each of these pathways converges into the terminal pathway, beginning with C5b and resulting in the formation of the membrane attack complex (MAC).

convertase in the alternative pathway. This convertase then cleaves the C5 protein, initiating the formation of the membrane attack complex (MAC).

The lectin pathway

The lectin pathway of complement activation begins when mannose-binding lectin (MBL) or ficolin proteins bind to specific carbohydrate targets on the surfaces of pathogens. This binding triggers the association of MBL-associated serine proteases (MASPs) with MBL. Structurally and functionally, MASP-1 is analogous to C1r, and MASP-2 mirrors the C1s protein of the classical pathway. Once activated, MASP-1 facilitates the activation of MASP-2, which then cleaves C2 and C4, forming the C3 convertase (C4b2a). This step initiates a cascade of events similar to those in the classical pathway, leading to further complement activation.

Common terminal pathway

The common terminal pathway of complement activation begins with the action of the C5 convertase, which is generated by the three main pathways. This enzyme catalyzes the activation of the late-stage complement components—C6, C7, C8, and C9, proteins that do not possess enzymatic activity but are essential for forming the membrane attack complex (MAC). The C5 convertase cleaves C5 into two fragments: C5a and C5b. C5a is similar to C3a and plays a role in inflammation, while C5b initiates the assembly of the MAC. C5b sequentially binds C6, C7, C8, and multiple C9 molecules, culminating in the formation of the C5b678-poly9 complex. This complex polymerizes C9 at the binding site with the C5b678 assembly to create a pore in the plasma membrane.

C1 esterase inhibitor and its effects on heart transplantation

C1 esterase inhibitors (C1-INH) play a critical role in moderating complement activation, particularly in the context of heart transplant surgery. The classical C1 pathway, significant in conditions such as anemia or reperfusion injury in myocardial infarction or heart failure patients, is inactivated by C1-INH. This inhibition occurs as C1-INH binds to and inactivates the C1r and C1s proteases within the C1 complex (Figure 2). Similarly, in the lectin pathway, C1-INH targets and disables the MASP1 and MASP2 proteases in the MBL complex (Figure 2). By inhibiting these key pathways, C1-INH effectively reduces inflammatory responses and immune-mediated damage controlled by the complement system, thereby mitigating complications associated with transplant rejection in organ transplant recipients.

On the other hand, compared to other complement-mediated immunosuppressants, C1-INH does not significantly inhibit the formation of the membrane attack complex, due to a compensatory increase from the alternative pathway. Consequently, C1-INH does not adversely affect the immune defense against bacteria, particularly Neisseria infections. Furthermore, C1 esterase inhibitors limit ischemia-reperfusion injuries by reducing the deposition of C4d and C3b proteins, thus preserving tissue structural integrity and decreasing the concentration of inflammatory and chemotactic mediators such as C3a and C5a. This reduction leads to decreased cytokine production and inflammation [10, 11]. Notably, C1-INH also impacts the blood coagulation pathway and activates kallikrein by inhibiting activated coagulation factors XII and XI, as well as thrombin protein. These actions help reduce blood clotting in small vessels, thereby limiting complications from thrombotic microangiopathy [12].

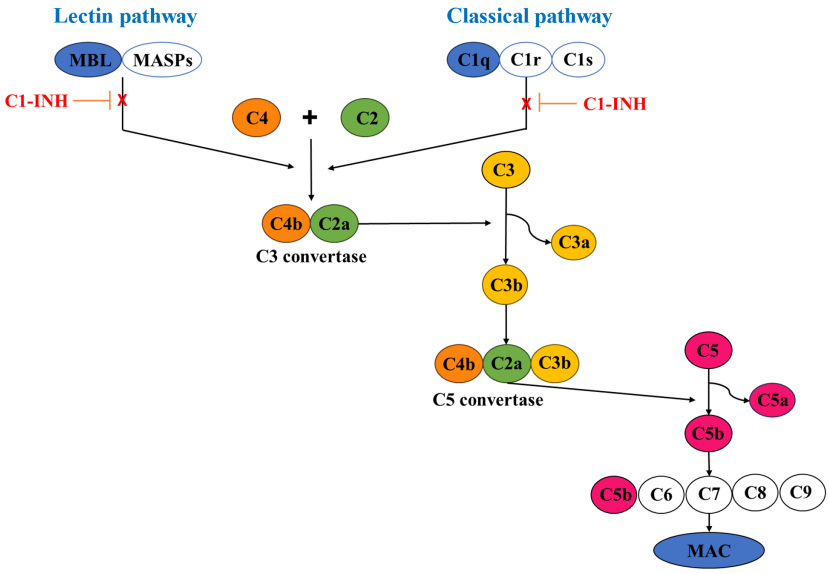

Figure 2: Mechanism of action of C1 esterase inhibitors on the classical pathway and the Lectin pathway in activating the complement system. TC1-INH: C1 esterase inhibitor. MBL: Mannose-binding lectin. MASP: mannose-binding lectin-associated serine protease.

Additionally, C1-INH has been demonstrated to reduce the accumulation and infiltration of neutrophils in target tissues, while also inactivating the complement pathway, thus minimizing damage caused by ischemia-reperfusion [11].

C1 esterase inhibitors have proven effective in reducing transplant rejection in kidney and lung transplant recipients [13, 14]. In heart transplant patients, C1-INH has been shown to improve right ventricular function when administered directly into the coronary artery [15]. Through these mechanisms of action and evidence from clinical experiments, the promising potential of C1 esterase inhibitors is evident in mitigating complications of transplant rejection and enhancing the prognosis for organ transplant patients, particularly those undergoing heart transplants.

Conclusion

C1 esterase inhibitor has proven effective in preventing graft rejection in organ transplantation. Further studies are needed to explore its efficacy in heart transplants to improve long-term outcomes.

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Ethics approval and consent to participate

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Competing interests

None to declare.

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