

The Role Of Complement In Antibody Mediated Rejection Of Kidney Transplantation

Getu Hurisa, Chala Mohammed, Lama Yimer

Wollega University, College of Health and Medical Sciences, School of Veterinary Medicine, Ethiopia
Corresponding Author: Dr. Chala Mohammed, Wollega University, School of Veterinary Medicine, P.O. Box: 395,
Ethiopia.

Tel: +251-913-11-5805.

Abstract: This review, gives the current understanding of complement in the immunology of kidney transplantation and describe studies demonstrating that blockade of terminal complement activation can prevent in antibody mediated rejection sensitized renal transplant recipients. It provides a broad understanding of the pathogenesis of antibody mediated rejection, recent advances in its therapy, and future directions. It also discusses about complement pathway and mechanisms of activation in kidney transplantation, biological effects of complement, the role of complement in kidney transplantation and treatment of antibody mediated rejection in kidney transplantation and complement inhibitors. More detailed studies with existing agents, such as eculizumab, will likely improve our understanding of the role of terminal complement activation in acute and chronic antibody mediated rejection. General the role of complement in antibody mediated rejection of organ allografts has progressed steadily over the past decade. There for the following recommendation are forwarded: during kidney transplantation, antibodies and blood group antigen of donor and receiver should be diagnosed, kidney transplanted should be done between healthy kidney individuals and the elimination of circulating antibodies and suppression of antibody production by B lymphocytes or plasma cells.

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1 Introduction

Organ transplantation is a surgical procedure to replace a failing, diseased organ with a healthier donor organ such as a heart, liver, kidney or lung. Donor organs can come from deceased donors, which is always the case in heart transplants, or from living donors, which can happen in kidney, liver, and rarely, lung transplantations. It is the last resort for a person with a failing or diseased organ. Usually, other treatments are tried first, such as medications for the underlying disease, or changes to diet and lifestyle [1].

Healthy kidneys clean blood by removing excess fluid, minerals and wastes. They also make hormones that keep your bones strong and your blood healthy. When kidney fail harmful wastes build up in body, blood pressure may rise and body may retain excess fluid and not make enough red blood cells. When this happen, you need treatment to replace the work of failed kidneys [2].

Kidney transplantation is a procedure that places a healthy kidney from one person in to another. They one new kidney takes over the work of two failed kidneys. The science of kidney transplantation has progressed considerably in the past half-century largely because of an improved understanding of the role of the immune system in allograft rejection, the disentanglement of the molecular mechanisms

underlying graft failure, and better management of immunosuppression [3].

Renal transplantation remains the preferred treatment of choice for pediatric patients with advanced chronic kidney disease due to better patient survival, growth, and quality of life compared to chronic dialysis [4, 5 and 6]. Kidney transplantation has become the preferred treatment for qualified patients with end stage of renal disease. Successful kidney transplant is more cost-effective than maintenance dialysis, and more importantly, it provides better quality of life and prolongs life [7, 8 and 9].

Immune system is equipped to identify foreign objects in your body as threats, and to try to eliminate them. This process allows your body to fend off bacteria and viruses, but it also kicks in when you receive a donor organ transplant, and can lead to organ rejection. Some degree of rejection occurs with every transplant, but it may or may not cause physical problems. It is common for a transplant recipient to experience one acute episode of rejection in the first year following surgery, but it can also occur years after. Of real concern to organ recipients is a condition called chronic (ongoing) rejection, in which the transplanted organ gradually loses its ability to function [10].

Conventional therapeutic approaches to AMR have minimal impact on mature plasma cells, the major source of antibody production. Emerging therapies include bortezomib, a proteasome inhibitor, and eculizumab, an anti-C5 antibody. In several reports, bortezomib therapy resulted in prompt reversal of rejection, decreased titers of donor-specific antibodies (DSA), and improved renal allograft function. Eculizumab also reversed AMR and prevented its development in patients with high post-transplantation DSA levels [11].

Complement is a central part of the innate immunity that serves as a first line of defense against foreign and altered host cells. The complement system can be initiated depending on the context by three distinct pathways – classical (CP), lectin (LP), and alternative (AP), each leading to a common terminal pathway. In a healthy individual, the AP is permanently active at low levels to survey for presence of pathogens [12, 13 and 14].

So far, many works had been reported regarding on the role of compliment in antibody mediation rejection in kidney transplantation. But since this practice is so many important no its technologies expanded to the world more over to developing countries like Ethiopia. Therefore, the objective of this paper is:

- ❖ To review on the role of compliment in antibody mediation rejection in kidney transplantation.
- ❖ To understanding of compliment in the immunology of kidney transplantation.
- ❖ Treatment of antibody mediated rejection in kidney transplantation.

2 Historical Perspective Of Compliment And Antibody Mediated Rejection In Kidney Transplantation

From the 1950s to the mid 1980s, the major clinical problem to be overcome in transplantation medicine was acute cellular rejection of the allograft. In these early years, acute cellular rejection of the organ was extremely common, difficult to treat and the primary cause of graft loss after kidney transplantation. In 2010, the list of Canadians waiting for an organ transplant grew to over 4,000 people. In the previous year, 1,803 transplants were performed. Also, unfortunately, 195 Canadians died while waiting for an organ transplant in 2009 [12].

The term "complement" was coined by Paul Ehrlich to describe the activity in serum, which could "complement" the ability of specific antibody to cause lysis of bacteria. Complement historically refers to fresh serum capable of lysing antibody coated cells [15]. First and foremost was the discovery that peritubular capillary deposition of C4, a product of complement activation, was associated with graft loss

and seen most often in sensitized transplant recipients attack complex is assembled as a result of complement activation and causes necrosis and endothelial cell detachment from the basement membrane, characteristic histological features of antibody mediated rejection (ABMR) [16].

The most common approach historically was total avoidance of transplantation in patients in whom DSAs were detected. Until the mid 1980s, the primary method of detecting DSAs was the complement dependent cytotoxicity assay [17]. Emerging evidence over the past improved, methods of detecting antibody mediated injury in the allograft lagged behind. Despite multiple attempts by researchers, immunohistological techniques used historically (or developed since) have not reliably demonstrated the presence of either immunoglobulin(G or M) in renal allografts with suspected antibody mediated rejection [18]. The development of a reliable C4d immunostaining technique in 1991 was a major advance in this research area as it provided indirect evidence of DSA binding to the allograft and suggested a role for complement activation in AMR [19].

De novo DSA are mainly directed against class II human leukocyte antigen(HLA), and are associated with worse prognosis than class I HLA. DSA assays use either cell-based or solid phase tests. The cell based tests include the ischemia reperfusion injury) and the flow cytometric cross match assay. The solid phase tests include enzyme-linked immunosorbent assays and multianalyte bead test by flow cytometry (Luminex technology). Only the cell-dependent cytotoxicity (CDC) and solid phase tests have been approved by the US Food and Drug Administration(FDA) for detection of HLA antibodies tests have been approved by the US Food and Drug Administration (FDA) for detection of HLA as qualitative assays [20].

The development of a reliable technique for detecting activation or deposition of complement factors in renal allografts was a major advance; however, whether complement was a primary factor in organ allograft rejection or merely a non-specific factor was still unclear. The development of techniques to identify the specificity and levels of DSAs helped clarify the link between complement and AMR [21].

3 The Knowledge Of Complement System And Its Role In Kidney Transplantation

The ability of pattern-recognition molecules to bind foreign markers such as pathogen-associated molecular patterns is central to the innate immune defense. One such defense mechanism is complement, which is capable of recognizing molecular patterns associated with microbes and apoptotic or necrotic

cells. Recognition causes activation of proteolytic enzyme cascades, resulting in cleavage of the complement proteins C3, C4, and C5. Fragments of these proteins have important effect or functions through binding to host cell receptors and pathogen surfaces [22].

The complement system is part of innate immunity, and it acts as a first line of defense against pathogens and a guardian of the host homeostasis. It is composed of at least 30 proteins, mostly synthesized in the liver, which typically circulate as inactive state as of the protease elements is maintained by the presence of several inhibitors. Complement activation initiates a cascade reaction, which leads to the cleavage of inert plasmatic components that generate bioactive components, including C3b, C3a, C5a, and C5b-9, with proinflammatory, chemo-attractant, and cell-damaging functions. Complement activation is tightly regulated to protect host cells from its toxic effects [13].

3.1 Biological Effects of Complement

3.1.1. Cytolysis

Destruction of target cells by lysis of the cell membrane. This is termed cytotoxicity in the case of nucleated cells, hemolysis for red blood cells, or bacteriolysis in the case of bacteria. Not all bacterial and eukaryotic cells are susceptible to complement-dependent lysis. Each functional membrane attack complex (MAC) is sufficient to lyse by colloid osmosis in the membrane of metabolically inert cells, like erythrocytes or liposomes Gram-negative bacteria are also susceptible to complement killing, in particular the meningitis causing *Neisseria* species. Individuals deficient in terminal complement components are at increased risk for recurrent meningitis. Gram-positive bacteria have an extremely thick cell wall that MAC cannot penetrate leaving them resistant to complement elimination [23].

3.1.2. Anaphylotoxin activity

The anaphylatoxins, C3a and C5a, are constantly released during complement activation. These small peptides play a critical role in supporting inflammation and activation of cells that express anaphylatoxin receptors [24]. To enhance inflammation, anaphylatoxins recruit immune cells to the site of complement activation and induce oxidative bursts on macrophages [25], eosinophils [26], neutrophils and stimulation of mast cells to release histamine and other substances, resulting in increased capillary permeability and local accumulation of fluid in the tissue [27].

3.1.3. Chemotaxis

The complement system is a major contributor to acute inflammation. For example, activation of the complement system by any of its pathways generates several potent chemotactic peptides, including C5a

and C5b67. It is mechanism of attraction of polymorphonuclear neutrophils (PMN's) to a local site of inflammation. The directed migration of neutrophils is called chemotaxis. Bacterial invasion and the resulting tissue damage generate many different attractants. These include a peptide called C5a, generated by activation of complement a peptide called fibrinopeptide B, derived from fibrinogen and a peptide called azurocidin related to the defensins [28].

3.1.4. Opsonization

Facilitation of phagocytosis by macrophages or PMN's via cell-surface receptors specific for complement components ("complement receptors"). C3b bound to a microbial surface is a very potent and effective opsonin since phagocytic cells possess CR1. Thus, C3b-coated organisms will bind strongly to these cells and under go type II phagocytosis. If for some reason these organisms cannot be ingested, then neutrophils may secrete their lysosomal enzymes and oxidants and oxidants into the surrounding tissue fluid [29].

3.1.5. Tissue damage

Both the lytic complex and the inflammatory PMN's can cause considerable damage to normal tissues, for instance in an Arthus Reaction or in Immune Complex Disease [30].

3.2 Complement Pathway and Mechanism of Activation in Kidney Transplantation

Complement a group of serum proteins which can be activated (fixed) by antigen-antibody complexes or other substances, which may result in lysis of a microbial target, or a variety of other biological effects important in both innate and adaptive immunity. The majority of these proteins are produced by the liver. The process of complement fixation requires specific protein/protein interactions, it involves proteolytic cleavages and conformational changes of proteins, and new biological activities are generated as a result [31].

Complement activation is a tightly regulated process that requires sequential and organized activation of proteins in order to form the effector molecules involved in host defense, pathogen clearance, and modulation of the inflammatory response. The complement includes three different path ways of activation and multiple bioactive molecules. It is a highly complex system that is regulated by processes operating at various levels in a fluid phase (plasma) and on cell surfaces [32].

Complement activation is tightly regulated so as to prevent by stander damage to self cells. This regulation is accomplished through the expression of membrane bound and soluble complement regulating proteins. Decay accelerating factor (DAF or CD55) is a glycoposphatidylinositol anchored, membrane bound complement regulator that accelerates the decay

of cell surface assembled C3 converters. DAF limits downstream complement activation and restricts production of the mentioned cleavage products [33]. There are three pathways present in activation of complement (Classical, Alternative and Lectin pathway). These three pathways primarily differ in their recognition target, which includes antibodies in the classical pathway (CP), carbohydrates in the lectin pathway, and a permanent low level activation in the alternative pathway (AP) [34].

3.2.1. Classical Path-way

Classical path-way is antibody-dependent complement fixation. This pathway is initiated by antigen/antibody complexes and requires heat sensitive complement components [35]. The classical pathway is triggered primarily by immune complexes (containing antigen and IgG or IgM) in the presence of complement components 1, 4, 2, 3, Ca⁺⁺ and Mg⁺⁺ cations. While IgG1, IgG2 and IgG3 (most effective) can activate complement, IgG4 is not able to activate at all. C1 is the first complement component to participate in classical pathway. It is composed of C1q, C1r and C1s. Binding of C1q to Ag-Ab complexes results in autocatalysis of C1r. The altered C1r cleaves C1s and this cleaved C1s is capable of cleaving both C4 and C2 [36].

Activated C1s enzymatically cleaves C4 into C4a and C4b. C4b binds to the Ag-bearing particle or cell membrane while C4a remains a biologically active peptide at the reaction site. C4b binds C2, which becomes susceptible to C1s and is cleaved into C2a and C2b. C2a remains complexed with C4b whereas C2b is released. C4b2a complex is known as C3 convertase. C3 convertase, in the presence of Mg⁺⁺, cleaves C3 into C3a and C3b. C3b binds to the membrane to form C4b2a3b complex whereas C3a remains in the microenvironment. C4b2a3b complex functions as C5 convertase, which cleaves C5 into C5a and C5b [37].

Generation of C5 convertase marks the end of the classical pathway. C5b initiates the formation of membrane attack complex. C1qrs can also bind to a number of agents including some retroviruses, mycoplasma, polyinosinic acid and aggregated IgG, and initiate the classical pathway. The classical pathway has been implicated in the pathogenesis of complement driven IRI [40]. However studies in rodent models of renal IRI indicate a predominant role for the alternative pathway and the classical path way does not appear to impact reperfusion injury when tested in C4 deficient mice or RAG 1 deficient animals which are unable to generate IgM or Ig [38].

3.2.2. Alternative Pathway

In the plasma, during normal physiological conditions, the dominant active complement pathway is the AP. The AP monitors for pathogen invasion by

maintaining a low level of constitutive activation by a process known as tick-over [39]. Tick-over is the spontaneous hydrolysis of a labile thioester bond, which converts C3 to a bioactive form C3(H₂O) in the fluid phase. It begins with the spontaneous activation of C3 in serum and requires Factors B and D and Mg⁺⁺, all present in normal serum. A C3b-like molecule (C3i) is generated by slow hydrolysis of native C3. C3i binds factor B, which is cleaved by Factor D to produce C3iBb. C3iBb cleaves native C3 into C3a and C3b. C3b binds factor B, which is again cleaved by Factor D to produce C3bBb (now C3 convertase) [40].

If the generation of C3 convertase is difficult to follow, one may simply assume that C3 is spontaneously broken in serum to C3b, which is acted upon by Factor B to form C3bB. This is then cleaved by Factor D to form C3bBb. C3b has very short life and unless stabilized by membrane or molecule present on many pathogens, it is quickly inactivated. In the absence of such a molecule, it binds quickly to RBCs via the C3b receptor (CR1), and (DAF) prevents the binding of Factor B. Another serum protein, factor H, can displace factor B and bind to C3b. Binding of factor H makes C3b more susceptible to factor I, which then cleaves it into many fragments (iC3b, C3d, C3e). C3 convertase generated in the classical pathway is also regulated by DAF, CR1 and Factor I [41].

The alternative pathway provides a means of non-specific resistance against infection without the participation of antibodies and hence provides a first line of defence against a number of infectious agents. Some of the microbial components, which can activate the alternative complement cascade, include lipopolysaccharide (LPS) from Gram negative outer membranes, teichoic acid from Gram positive cell walls, certain viruses, parasites, heterologous red cells, zymosan from fungal and yeast cell walls and some parasite surface molecules. Aggregated immunoglobulins (particularly IgA), cobra venom factor (CVF) and other proteins (e.g. protease, clotting pathway products) also can activate the alternative pathway [42].

3.2.3. Lectin pathway

A third mechanism for the initiation of complement fixation has been described which depends on the presence of another normal serum protein known as the mannan-binding lectin. This protein is capable of binding to microbial carbohydrates containing terminal mannose residues, and consequently binding two other proteins, MASP-1 and MASP-2 (mannan-binding lectin-associated serum protease-1 and -2). The resulting complex has C4-convertase activity (i.e. it can bind and cleave C4), and the remainder of the complement cascade (C2, C3, C5

etc.) is activated just as in the case of the classical and alternate pathway. On the other hand, Factor B-deficient mice known to be defective in alternative pathway activation, show a marked reduction in functional and morphological injury induced by ischemia and reperfusion [39].

3.3 The Role of Complement In Kidney Transplantation

The role of complement in the biology of kidney transplantation is becoming more and more significant, but not only because we now have access to drugs inhibiting complement. After describing the main characteristics of complement biology, both activation of the complement cascade and the many regulatory factors, review the precise role of complement in kidney transplant biology. Complement activation has been involved in ischemia-reperfusion injury, in the recurrence of several diseases such as atypical hemolytic uremic syndrome, C3 glomerulopathies and antiphospholipid syndrome, as well as the process of antibody mediated rejection, either acute or chronic. The role of complement in various aspects of kidney transplantation has been outlined over the past several years [43].

3.3.1. Ischemia reperfusion injury

The role of complement has been increasingly involved in organ transplantation. For example, all kidneys suffer from IR (Ischemia Reperfusion) and delayed graft function but to a variable extent, from primary non function to the absence of clinical consequence [30]. Ischemia reperfusion injury (IRI) is a common mechanism of injury in a wide variety of conditions characterized by limited tissue perfusion. During the ischemic period, tissues are deprived of oxygen and nutrients required to maintain normal metabolism and energy homeostasis. As a result, cells in ischemic tissues become necrotic and release a variety of endogenous ligands known to stimulate innate immune responses [44].

Briefly, IR injury results from tissue hypoxia, mitochondrial damage, and ATP depletion, followed by the generation of free oxygen radicals upon reperfusion, which initially damage endothelium. Ensuing inflammation driven by TLR signaling and locally secreted cytokines, chemokines, and complement amplify the inflammation, resulting in tubular injury and kidney dysfunction. Early evidence implicating a role for complement in IR injury derived from mouse models in which complement deposition and loss of membrane-bound complement regulators were described during kidney IR injury and overexpression of Crry ameliorated IR injury [45 and 46].

The complement system has been strongly associated with the inflammatory response to IRI [47].

Although initially it was believed that the complement system was exclusively involved in responses to non self-antigens, recent research has provided a novel perspective into its intricate role in the sterile immune response to injury and tissue repair. Following IRI, the release of danger associated molecular patterns (DAMPs), neo antigen formation, and immune complex formation can activate the complement system by any of the three main pathways [48].

3.3.2. Antibody-mediated rejection

Kidney transplant rejections are classified into T-cell-mediated (acute cellular rejection; ACR) and antibody-mediated (humoral) rejection (AMR). AMR occurs in up to 20 - 30% of all acute rejection episodes following kidney transplantation and can co-exist with cellular rejection. The term 'AMR' defines all allograft rejections caused by antibodies directed against donor-specific human leukocyte antigen (HLA), blood group antigen (ABO), or endothelial cell antigens [11].

Antibody mediated rejection is a relatively rare but severe complication in kidney transplantation associated with increased risk of graft loss [49]. Physiologically, endothelial cells are adapted to cope with low levels of activated complement, but not complement hyperactivity. The level of DSAs in historical sera and at day 0 is predictive of ABMR, but recent findings also highlight the influence of complement hyperactivity on allograft survival. The presence of C1q-binding donor-specific anti HLA antibodies before or during the course of transplantation is an independent predictor of kidney allograft [50].

Antibody mediated rejection can present as an early acute process, often resulting from an anamnestic response, or as a late and chronic process due to de novo antibody production. In the acute phase, it is often preformed antibodies that cause early rejection. De novo DSA can also develop in the early post-transplant period, resulting in acute rejection. Patients with preformed DSA are at significantly greater risk of having an acute AMR and have significantly lower graft survival. The classification of AMR is based on clinical setting, underlying pathophysiological relationship to transplantation. There are three types of AMR [51].

Hyperacute antibody mediated rejection: hyperacute AMR is caused by preformed donor specific antibodies (DSA). It is rarely seen nowadays due to the routine use of pre transplantation cross-matching. It usually manifests shortly after the vascular anastomoses are established but it can be delayed up to 3 days. Histologically, the major findings associated with hyper acute AMR are neutrophil and platelet margination in glomerular and per tubular capillaries, red blood cell stasis, fibrin

deposition and thrombosis within the microvasculature, acute tubular injury and widespread hemorrhagic cortical necrosis. These changes depend on the interval between transplantation and biopsy or removal of the graft [52].

Acute antibody-mediated rejection:-The reported incidence of acute AMR varies in different centers depending on protocols for performing transplantation in highly sensitized patients and the methods used to detect DSA. Patients with acute AMR present with sudden onset of graft dysfunction that often arises in the first few weeks after transplantation. Presensitization is a major risk factor but most patients with AMR had a negative cross-match. There are three types of acute AMR: type I is acute tubular necrosis (ATN) like, type II is glomerular type, resembling thrombotic microangiopathy, and type III is vascular type with arterial inflammation [53].

The more frequent glomerular form of acute AMR is characterized by diffuse peritubular capillary staining for the complement component C4d. The histological appearance may show scattered glomerular, PTC and tubulointerstitial neutrophils or monocyte (macrophages). The vascular/arterial type is characterized primarily by necrotizing arteritis, with mural fibrinoid necrosis and variable inflammation in the artery wall, including lymphocytes, monocytes and neutrophils along with luminal thrombosis. This lesion typically results in cortical infarction with focal interstitial hemorrhage. In the vascular form of antibody-mediated rejection, IgG and occasional Ig accompanied by C3 can be found in the walls of arteries [54].

Acute AMR occurs because of antibody-mediated complement activation and eventual lysis of graft endothelium. As such, AMR is associated with C4d deposition in peritubular capillaries. C4d is the complement split product resulting from the cleavage of C4. C4d can then covalently bind to the vascular endothelium of the kidney graft [23]. In acute AMR, patients present with an acute loss of graft function, most often in the first few weeks after transplantation. The clinical presentation is indistinguishable from acute cellular rejection. It can also occur years after transplantation when immune suppression is decreased or stopped, either inatrogenically or because of non adherence by the patient [55].

Chronic antibody mediated rejection: Chronic AMR is a slow, progressive loss of graft function that usually develops > 1 year after transplantation. Several studies have shown that circulating anti-HLA class I or II antibodies, either donor reactive/denovo or non-donor reactive, are found in a substantial fraction of renal allograft recipients, and these are associated with later graft loss. Transplant glomerulopathy and

arteriopathy are the pathologic features that are usually attributed to alloimmune mechanisms [56].

Despite the successful treatment, more than 40% of patients with AMR will develop transplant glomerulopathy the major chronic histologic lesion associated with chronic antibody mediated damage. Chronic AMR is an insidious process associated with fluctuating levels of donor-specific Antibodies (DSAs) and results in irreversible structural damage. Clinically, it manifests as proteinuria, hypertension, and declining graft function over time [5].

3.3.3. Cell-mediated rejection

The role of complement in the pathogenesis of cellular rejection came from the observation that wild-type mice do not reject allograft from C3-deficient donors. During the interaction between T cells and antigen-presenting cells, the AP(Alternative Pathway) is activated, leading finally to enhanced T-cell proliferation and decreased T-cell apoptosis. On macrophages and dendritic cells, C3a and C5a interacting with their receptors upregulate innate cytokines. Interesting results suggest that complement is an important molecular intermediary explaining how CD4 cells provide help to CD8+ cells. It is also important to stress the role of complement in T regulator cells [20].

3.3.4. Antiphospholipid syndrome

The complement activation in antiphospholipid syndrome, which is a rare but potentially devastating disease that may recur after kidney transplantation [57]. Murine models provide convincing evidence of a role of complement in fetal loss, the induction of thrombosis, and endothelial cell activation induced by antiphospholipid antibodies [58].

3.4 Treatment of Antibody Mediated Rejection in Kidney Transplantation and Complement Inhibitors

Treatment of humoral-mediated acute graft rejection differs from that of cell-mediated rejection; it involves the elimination of circulating antibodies and suppression of antibody production by B lymphocytes or plasma cells. Knowledge of the mechanism of injury in AMR has provided insights to therapeutic interventions. AMR involves the production of high levels of DSA by plasma cells [59].

Theoretically, it is possible to inhibit complement activity either by interacting with some pivotal complement fragments, such as C3 or C5 (compstatin, humanized Ab against C5), increasing the inhibitory capacity of regulatory proteins using soluble recombinant versions of membrane-bound proteins, such as FH (mini FH, TT30) or CR1 (sCR1, TT10, APT070), or inhibiting serine proteases (C1 inhibitor, anti-MASP2) [60].

Treatment modalities in AMR include [17]: Elimination of circulating antibodies (Plasmapheresis)

and Immunoabsorption), Suppression of remaining antibodies (IV infusions of immunoglobulins and Mycophenolatemofetil), Blocking antibody production, B lymphocyte depletion (Glucocorticosteroids), Anti CD20 antibody rituximab, Anti thymocyte globulin and Splenectomy), Suppression of T cell response (Anti thymocyte globulin, Mycophenolatemofetil) and Calcineurin inhibitors), Plasmocyte depletion and apoptosis (Protein synthesis inhibitor bortezomib), Complement inhibition (Anti C5 antibody eculizumab and Recombinant C1 inhibition) [28].

3.4.1. Eculizumab

Eculizumab is a humanized monoclonal antibody that inhibits complement fraction C5 preventing formation of terminal activation products C5a and MAC (C5b-9). Eculizumab has been approved by the FDA for the treatment of paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS). However, it has received major interest in the field of transplantation for the treatment of AMR and prophylactically in the prevention of post-transplant aHUS in kidney transplant recipients. A recent review summarizes the use of eculizumab for the prevention AMR and aHUS in kidney transplantation [61].

It has been administered to several kidney transplant recipients with recurrence of C3 glomerulopathy with inconstant efficacy, [40] anti phospholipids syndrome and even the catastrophic form of this disease, and very promising results were reported. At the Mayo Clinic, used eculizumab at the time of transplant to demonstrate that incomplete complement activation and blockade of terminal complement generation by eculizumab prevented the development of AMR in patients who developed high levels of DSA post transplant [48].

Eculizumab has used in kidney transplantation to treat or prevent HUS recurrence. This drug is efficient in patients with aHUS of their native kidneys or transplanted kidneys, in very active disease, and disease of long-term duration in patients maintained on plasma exchanges. The main experience in kidney transplantation was reported. The proportion of patients with complement mutations or anti-complementary FH antibodies was approximately 70% of patients with post transplant HUS [33].

Notably, patients with aHUS recurrence in their transplant kidney had significantly lower improvements in renal function compared with patients with aHUS on their native kidneys, which was likely due to worse renal function at the beginning of the study and a more delayed instauration of eculizumab. Trials are currently on for the prevention of I/R injury and delayed graft function using

eculizumab as well as C1 esterase inhibitor in patients who received a deceased kidney donor [62].

3.4.2. Molecules inhibiting C1 esterase

Purified C1-esterase inhibitors, which are used in the treatment of hereditary angioedema, have been used in small groups of patients to treat acute ABMR [33] or desensitize patients, and good safety profile and encouraging preliminary efficacy data are reported [63].

3.4.3. Rituximab

This is a humanised mouse monoclonal antibody that targets CD20, which is expressed on the majority of B cells. However, most plasma cells lack CD20 and are unaffected by Rituximab. Hence, its role will be as an adjunctive treatment. A recent single centre study compared outcomes in 24 cases of ABMR treated with either high dose IVIg (2g/kg for four doses) versus plasmapheresis plus IVIg (100mg/kg) for four treatments followed by IVIg (2g/kg for four doses) and two doses of rituximab (375mg/m²). Improved 3-year survival (92% vs. 50%) and significantly reduced DSA at 3 months was observed in the plasmapheresis/IVIg/rituximab group [64].

3.4.4. Promising complement inhibitors are in the pipeline

More than 20 complement therapeutic are currently in development [65]. Complement offers many intervention points, from proteases that drive the activation cascade to anaphylatoxins that mediate inflammatory responses. Theoretically, it is possible to inhibit complement activity by interacting with some pivotal complement fragments, such as C3b (compstatin or cp40), C5 (as eculizumab), and Factor D (humanized Ab, FD), increasing the inhibitory capacity of regulatory proteins with soluble recombinant versions of membrane bound proteins, such FH or inhibiting serine proteases [66].

4 Conclusion And Recommendations

General the role of complement in antibody mediated rejection of organ allografts has progressed steadily over the past decade. Clinical trials with the C5 antibody, eculizumab, have established a role for terminal complement in the development of acute antibody mediated rejection. The complement system is now firmly established as a pervasive, multifaceted mediator of transplant injury in animal, and studies from multiple groups have largely confirmed that these newly recognized mechanisms apply to human transplant recipients. Kidney transplantation success of translational immunology, along with the development of pharmacologic agents that block human complement components and receptor. None of these agents has a significant effect on the major source of antibody production: namely, the mature plasma cells. There is now emerging evidence that

protean some inhibition with bortezomib can target mature plasma cells, inducing apoptosis with reversal of AMR decrease in DSA titer and improved graft function. Bortezomib and eculizumab may play a major future role in AMR therapy.

Based on above conclusion the following recommendations are forwarded:

- ❖ During kidney transplantation, antibodies, blood group antigen of donor and receiver should be diagnosed.

- ❖ Kidney transplantation should be done between healthy kidney individuals.

- ❖ It should be prevent the formation of membrane attack and inhibitor antibody production.

- ❖ The elimination of circulating antibodies and suppression of antibody production by B lymphocytes or plasma cell in normal.

Corresponding Author:

Dr. Chala Mohammed, Wollega University, School of Veterinary Medicine, P.O. Box: 395, Ethiopia.
Tel: +251-913-11-5805.

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