The emerging role of complement inhibitors in transplantation

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The role of complement in the biology of kidney transplantation is becoming more and more significant, especially 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, we will 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. There are many potentially interesting drugs interfering with complement inhibition that have been or may be studied in kidney transplantation. Currently, the bulk of data concerns eculizumab, a monoclonal antibody blocking the complement cascade at the C5. Its efficacy has been demonstrated in the treatment and prevention of recurrence of atypical hemolytic uremic syndrome with an overall good safety profile. Although it has been reported to be efficacious to prevent antibody-mediated rejection, properly designed trials are currently being performed to state this efficacy. In addition, randomized trials are, in the process, regarding the prevention of ischemia–reperfusion injury after kidney transplantation.

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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. 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 pro-inflammatory, chemo-attractant, and cell-damaging functions. Complement activation is tightly regulated to protect host cells from its toxic effects.[1] A set of at least seven proteins in plasma (C1 INH, C4b-binding protein, factor H, and factor I) or cell membranes (decay-accelerating factor, membrane cofactor protein, and CR1 (CD35)) modulate the complement proteins and protect host cells and tissues from complement damage. It has become more and more obvious that the 'classical' conception of complement as a first line of defense against pathogens is too restrictive, and complement has a major role in several diseases that involve the kidney and influences the outcome of kidney transplant.[2,3]

The present article emphasizes the emerging knowledge of the relative contribution of the complement activation pathways to transplanted kidney tissue injury and focuses on the role of complement inhibitors in kidney transplantation.

THE COMPLEMENT SYSTEM

Schematically, the complement includes three different pathways of activation and multiple bioactive molecules (Figure 1). It is a highly complex system that is regulated by processes operating at various levels in a fluid phase (plasma) and on cell surfaces.[4] 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).

Antigen–antibody complexes in the CP activate the C1 component, which associates a pattern recognition molecule, C1q, and a heterotetramer of C1r and C1s proteases. Hexameric clustering of immunoglobulin G (IgG) to the target surface elicits a mechanical stress on the C1 complex that triggers the conversion of C1r and C1s into active proteases and the generation of the CP C3 convertase, C4b2a, after the cleavage of the next two reacting components of the

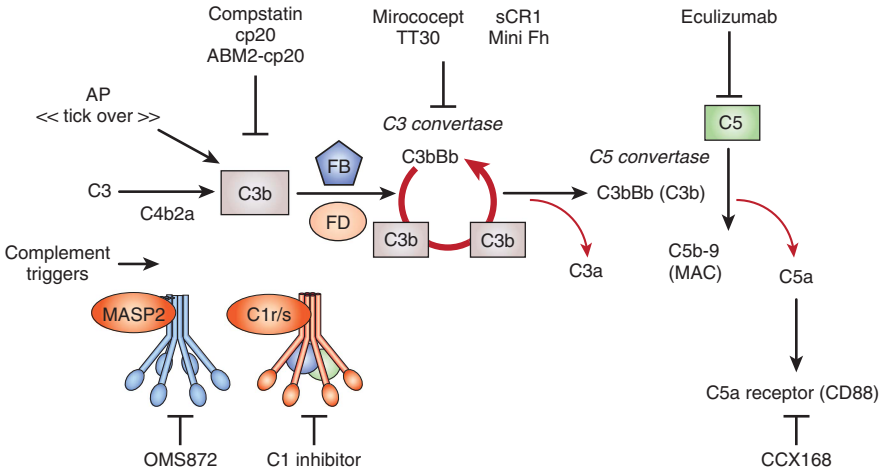

Figure 1 | The complement cascade with the target values for therapeutic drugs. The complement cascade includes the classic, alternative, and mannan-binding lectin pathways. A complex series of enzymatic proteins that are triggered in a cascade manner leads to the formation of the classical pathway C3 convertase (C4b2a) and the alternative C3 convertase (C3bBb). The C3 convertases cleave C3 into C3a and C3b. C3b binds to other C3 convertases to form C2a4b3b and C3bBb. C3b is also known as C5 convertase. C1 inhibitor is a suicide inhibitor that inhibits C1r and C1s. Soluble CR1 is a recombinant protein that inhibits C3 and C5 convertases. The peptide compstatin or the chimeric peptide Cp 20 or ABM2-Cp20 binds C3b and inhibits the activation of alternative pathway (AP). The anti-human C5 (eculizumab) blocks C5 cleavage. TT30 (a fusion protein between CCP1-4 FH and CCP1-4 CR2), mini FH (fusion protein between CCP1-4 FH and CCP19-20FH), and APT070 (Mirococept) are three short consensus domains of human CR1 with a membrane-targeting amphiphilic peptide that regulates C3 convertase. The antagonist of human C5aR/CD88 (CCX168) blocks the interaction between C5a and its receptor.

CP, C4 and C2. For example, C1q binds to the Fc portion of the pretransplant or *de novo* donor-specific anti-human leukocyte antigen (HLA) antibodies (DSAs), mainly IgGs, particularly IgG1 and IgG3, and activates the CP.[5]

Activation of the lectin pathway occurs after the binding of five different lectin pathway-specific carbohydrate recognition molecules, such as mannan-binding lectin and ficolins-associated serine proteases, particularly MASP2, to carbohydrate residues on microorganisms. Subsequently, complements C4 and C2 are cleaved, and the CP C3 convertase C4b2a is formed. Mannan-binding lectin binds to altered-self endogenous ligands that arise in pathological conditions, such as ischemia/reperfusion (I/R) injury, which leads to lectin pathway activation.[6]

No specific initiation is needed for the AP. It is constantly activated at low levels by the 'tick-over' of C3, which includes two proteins, Factor B and Factor D, that lead to the creation of the AP C3 convertase, C3bBb. C3bBb is a short-lived complex, and stabilization of this complex by properdin (the only positive regulator of the complement system) is required to ensure an efficient host defense. The convergence point of all three pathways is the cleavage of C3 into the active covalently bound C3b to cells and the liberation of the anaphylatoxin C3a into the circulation. The AP amplifies the level of C3b deposition on the target and the generation of C3a. This loop is the heart of the complement cascade.

C3b binds to the C3 convertase of the CP or the AP to form the C5 convertases, C4b2a (C3b)n and C3bBb (C3b)n, respectively, which then cleave C5. Cleavage of C5 leads to the generation of the anaphylatoxin C5a, the formation of sC5b9 in the circulation, and the insertion of the membrane attack complex on the cell surface. The AP is the most efficient pathway, and it is responsible for >80% of membrane attack complex formation on target cells. Anaphylatoxins C3a and C5a recruit phagocytes at the site of complement activation and generate an inflammatory environment.

Complement amplification depends on the balance between C3 convertase formation rate, which upregulates C3 cleavage, and the C3 breakdown cycle that downregulates it. Fluid phase and membrane-bound proteins regulate the complement system to prevent excessive activation of primarily the AP. Factor H (FH) is a major regulatory protein in plasma that efficiently controls the amplification loop of complement pathways. FH binds C3b and polyanionic surface markers to prevent the formation of the C3 convertase and induce its dissociation. FH is a cofactor for C3b proteolysis by Factor I. The C1 inhibitor specifically binds to and inactivates C1r and C1s, and therefore this inhibitor tightly regulates CP activation. The C4 binding protein C4bp increases the decay of C3 convertase in the CP, and Factor I inactivates C4b to C4d. The covalently linked C4d to the endothelium surface is an inactive stable degradation product that provides little C4 activation. Cell surface membrane cofactor protein and CR1 limit the number of active convertases by acting as cofactors for Factor I-mediated cleavage of C3b and C4b to their inactive products, iC3b/C3dg and C4d, respectively. Finally, the decay-accelerating factor inhibits the assembly or membrane insertion of the membrane attack complex complex and promotes the dissociation of the AP and CP C3 convertases with CR1.

COMPLEMENT IN KIDNEY TRANSPLANTATION

The role of complement in various aspects of kidney transplantation have been outlined over the past several years: I/R injury,[6] antibody-mediated rejection (ABMR),[2] recurrence of atypical hemolytic uremic syndrome,[7] C3 glomerulopathy,[8] antiphospholipid syndrome,[9] and the accommodation phenomenon[10] in ABO-incompatible transplantation.

I/R injury

The role of complement has been increasingly involved in organ transplantation. For example, all kidneys suffer from I/R and delayed graft function but to a variable extent, from primary non-function to the absence of clinical consequence.[11] Schematically, a part of this injury is complement dependent and blockade of complement could protect the organ.

Following endothelial damage secondary to I/R, inflammation occurs through cytokines, chemokines, and complement activation leading to tubular cell injury. In mouse models, I/R induces complement deposition and loss of complement regulators on the cell membranes. These lesions are decreased by every condition decreasing complement activity (such as complement-deficient mouse, C3, and/or C3-deficit) and increased by every condition leading to a deficit in complement regulators. Blockade of complement receptors present on both tubular cells and circulating leukocytes (C3aR, C5aR-deficient mice) also attenuates the I/R injury.

In human transplantation, more indirect evidence suggests a role of complement with the increased levels of soluble C5b-9 detected after reperfusion of deceased donor kidneys but not in living donor kidneys, and higher expression levels of complement genes in biopsies obtained at implantation in deceased donor kidneys (reviewed in Cravedi and Heeger[11]).

Schematically, in humans, the exquisitely IR-sensitive tubular cells produce C3 leading to the activation of the C5 convertase, the release of C3a and C5a recruiting inflammatory cells, whereas tubular cells are injured by the C5b-9 complex. It is currently admitted that the lectin pathway is the main activation pathway, whereas the AP amplified the injury. The role of the CP is less clear.[6]

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 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.[11] However, even though there is a lot of intense research on these fascinating matters, the clinical applications seem to be less immediately obvious than in delayed graft function or ABMR prevention except maybe with C5aR blockers.

Antibody-mediated rejection

Historically, two dates are important in outlining the role of complement in ABMR. First, Patel *et al.*[12] demonstrated the deleterious impact of complement-dependent lymphocytotoxic anti-HLA antibodies in their seminal paper in 1969, which established the cross-match test that remains a reference in transplantation currently. Activation of the CP because of immune-complex antigen combination (major histocompatibility complex molecules, ABO-blood group antigens) and IgG antibodies called DSAs initiates the ABMR process. Second, Feucht *et al.*[13] described the deleterious impact of the presence of the complement C4d component on peritubular capillaries using immunofluorescence in 1991. This description led to the first definition of ABMR in the Banff classification, in which the presence of C4d on peritubular capillaries was mandatory. After the binding of DSA to C1q, freshly cleaved C4b by C1s binds covalently to the activating surface near the site of initial activation. C4d staining in kidney transplant biopsies is performed using immunofluorescence or immunohistochemistry with an anti-human C4d antibody that recognizes the C4d region of the C4, which corresponds to the active C4b and/or inactive C4d. Recently, histological data and gene transcript analyses demonstrated that C4d positivity was not absolutely necessary to define ABMR. This observation created a new category of ABMR, called C4d-negative ABMR. Notably, the intensity of C4d positivity remains useful to grade the severity of ABMR.[14] C4 is central to activation of the CP, but its role in transplant outcome is not clear. The absence of C4d staining may be due to technical reasons or a low level of complement CP activation but efficient AP loop amplification. Regardless of the initial activation pathway, amplification at the C3 convertase step occurs through the AP. Genetic diversity of C4 may explain some cases of C4d-negative ABMR because of hereditary low levels of C4 in the circulation. Neither variation in the number of copies of the C4 genes nor plasma C4 concentration impacts the outcome of allograft rejection, which argues against a potential diagnostic benefit from recipient and donor C4 genotyping for risk stratification.[15]

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.[2] Sicard *et al.*[16] recently reported that the detection of C3d-binding DSAs may have a higher prognostic value than the presence of C1q-binding DSAs. These observations demonstrated that the

level of complement activation plays a major role in prognosis. The absence of C3b binding DSA in the presence of C1q binding DSA *in vitro* suggests that complement activation *in vivo* also stops at the level of C4 without C3 activation. A more recent systematic review of the role of C4d in ABMR confirmed the modest sensitivity compared with microcirculation inflammation or solid-phase DSA assays on diagnosis.[14]

Generation of the proinflammatory anaphylatoxin C5a is a major factor in graft injury because C5a attracts inflammatory cells and induces endothelial cells to increase the expression of adhesion molecules, such as endothelial cell selectin (E-selectin), vascular cell adhesion molecule 1 and intercellular adhesion molecule 1, and cytokines, such as interleukins 1 and 6. However, the mechanisms linking complement with the histological parameters that are observed in allograft rejection and graft loss are just starting to be elucidated. The recently identified top genes in ABMR include VWF endothelial transcripts, which are implicated after exposure of C5b9 at sub-lytic concentrations to endothelial cells.[17] *In vitro* C5b9 promotes the synthesis and secretion of pro-inflammatory molecules, such as C-C chemokine ligand 2 and C-X-C chemokine ligand 8, but it also triggers endothelial cell synthesis of tissue factor, loss of anticoagulant surface heparan sulfate proteoglycans, and cytoskeletal rearrangements, with consequent cell retraction and exposure of the procoagulant extracellular matrix. Thrombotic injury may dominate in severe cases of ABMR so that the rejection resembles thrombotic microangiopathy with diffuse vascular injury and thrombosis. Experimentals models showed that early blockade of complement activation by anti-C1s monoclonal antibody inhibits *in vitro* complement activation induced by DSA and that recombinant human C1-inhibitor can prevent acute ABMR in presensitized recipients.[5,18]

Recurrence of diseases that primarily involve the alternate pathway

Atypical hemolytic and uremic syndrome (aHUS) is emerging as the paradigm for diseases caused by an inefficient protection of the endothelium from complement attack. Indeed, $>50\%$ of patients carry mutations in FH, FI, FB, C3, and CD46 genes, which causes an uncontrolled activation of the AP. A large body of evidence has accumulated in the past decade that supports the dramatic efficacy of eculizumab in disease control, which opens the possibility of successful renal transplantation in aHUS patients.[19] The overall outcome of kidney transplantation in adults with aHUS before the eculizumab era was poor, with 7% deaths and 50% graft failure 5 years posttransplant in a large French cohort of aHUS patients.[20] Overall, poor graft survival is largely due to aHUS recurrence, which occurred in 68% of patients. The recurrence risk is major during the first year (accounting for 70% of recurrence), but decreases markedly thereafter. Genetic background strongly determines recurrence. Patients with mutations in complement factors have a threefold increase in post-transplant aHUS recurrence compared with aHUS patients without mutations.[7]

C3 glomerulopathy is a heterogeneous group of glomerular diseases that are associated with acquired or genetic abnormalities of complement AP components. It is characterized by predominant C3 deposits in the mesangium and along (in cases of C3 glomerulonephritis) or within (in cases of dense deposit diseases) the glomerular basement membrane. The clinical presentation is heterogeneous, with proteinuria (sometimes with nephritic syndrome), hematuria, hypertension, and renal failure. C3 glomerulopathies have a poor renal prognosis, with progression to end-stage renal disease in 50% of cases in the first decade after initial presentation. These patients have low serum C3 levels, which is attributed to the fluid phase activation of the AP in 50% of cases. Animal models confirmed the role of excessive C3 activation in the pathogenesis of C3 glomerulopathy. Some patients also exhibit increased sC5b9 in plasma, which highlights terminal pathway activation. The optimal treatment for these patients is not known. Moreover, the disease recurs after kidney transplantation in approximately 50% of cases, which increases the likelihood of graft loss.[8]

Antiphospholipid syndrome

There are also data that suggest complement activation in antiphospholipid syndrome, which is a rare but potentially devastating disease that may recur after kidney transplantation.[9] 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. However, few data document the role of complement in the development of antiphospholipid antibody syndrome in humans.

COMPLEMENT INHIBITORS

Theoretically, it is possible to inhibit complement activity either by interacting with some pivotal complement fragments, such as C3 or C5 (compstatin, humanized Ab again C5), increasing the inhibitory capacity of regulatory proteins using soluble recombinant versions of membrane-bound proteins, such FH (mini FH, TT30) or CR1 (sCR1, TT10, APT070), or inhibiting serine proteases (C1 inhibitor, anti-MASP2). There are two currently available complement inhibitors, a monoclonal antibody against C5 and a purified and recombinant C1 inhibitor (Table 1).

Eculizumab

Eculizumab is a recombinant fully humanized hybrid IgG2/IgG4 monoclonal antibody directed against the human complement component C5. It was engineered to minimize immunogenicity, Fc-mediated functions, and complement activation. Eculizumab binds C5 with very high efficacy and inhibits C5 cleavage by C5 convertase. The formation of C5a and C5b-9 is blocked, which prevents the pro-inflammatory, pro-thrombotic, and lytic functions of complement. The inhibition of complement activation at the C5 level

Table 1 | Examples of complement inhibitor drugs according to mechanisms of action[19,27,30–32]

Target pathway	Target of the drug	Drug	Description of the drug	Mechanism of action	Phase of clinical development
Derived from natural regulator					
AP	CD35 (CR1)	sCR1, TT10	Soluble form of recombinant CR1	Inactivation of C3b	Inconclusive results in cardiac surgery and in dense deposit disease
AP	CD35 (CR1)	APT070, Mirococept	Truncated CR1 with lipopeptide membrane	Inactivation of C3b	Clinical trial for preventing ischemia-reperfusion injury in the kidney allograft
AP	C3d on cells	TT30 (Alexion)	Fusion protein between CCP1-4 FH and CCP1-4 CR2	Inactivation of C3b	Preclinical
AP	FH	Mini FH (Amyndas)	Fusion protein between CCP1-4 FH and CCP19-20FH	Inactivation of C3b	Preclinical
AP	FH	r FH (Optherion)	Purified or recombinant FH	Inactivation of C3b	Preclinical
CP	C1 inhibitor	Berinert (CSL Behring), Cinryze (ViroPharma)	Purified or recombinant C1 inhibitor	Inactivation of C1	Drug approved for hereditary angioedema, clinical trial in Trx
Inhibition of protein-protein interaction					
Terminal and C5a pathways	C5 to C5 convertase	Eculizumab (Alexion)	Humanized monoclonal IgG2/4 antibody against C5	Inhibition of the cleavage of C5 to C5a and C5b	Drug approved for PNH, aHUS; clinical trials in complement-mediated diseases
AP	FD to C3bB	Lampalizumab (Roche)	Humanized monoclonal antibody directed against factor D	Inhibition of Factor B cleavage within the C3bB	Clinical trial in age macular degeneration (Phase 2)
AP	C3 to the C3 convertase	AMY-101 or Cp40 (Amyndas)	Derived product from compstatin: Cyclic peptide that binds C3	Inhibition of the C3 cleavage by the C3 convertase	Preclinical
C5a pathway	C5a to C5aR	CCX168 (ChemoCentryx)	Small-molecule antagonist of human C5aR/CD88,	C5a inhibition	Clinical trial in ANCA-associated renal vasculitis
LP	MASP2 to C4	OMS872 (Omeros)	Humanized monoclonal antibody again MASP 2	Inhibition of C4 cleavage	Clinical trial in atypical bleHUS (Phase 2)
Inhibition of protein synthesis					
Terminal and C5a pathways	C5	ALN-CC5 (Alnylam)	RNAi therapeutic targeting C5	Inhibition of the C5 synthesis by the liver	Preclinical

Abbreviations: aHUS, atypical hemolytic and uremic syndrome; ANCA, antineutrophil cytoplasmic antibody; AP, alternative pathway; CP, classical pathway; Ig, immunoglobulin; LP, lectin pathway.

creates an acquired functional C5 deficiency, and the risk of meningitis from Neisseria species is increased similarly to patients with genetically determined C5 deficiency. Therefore, prophylaxis with vaccination and antibiotics is mandatory. However, blockade of the complement cascade at the C5 level preserves the early components of complement, which are essential for opsonization of microorganisms and clearance of immune complexes.[21]

Eculizumab has been used mainly in the prevention of acute ABMR and treatment/prevention of aHUS recurrence and antiphospholipid syndrome in the kidney transplantation setting.

The role of eculizumab in preventing ABMR was reported by Stegall *et al.*[22] in a single-center, open-label study. Twenty-six highly immunized patients were desensitized according to local practice (mainly plasma exchanges) and transplanted with a living-donor kidney. The patients received eculizumab at days − 1 and 0, then weekly for 1 month and monthly for varying periods of time from 2 months to 1 year. These patients were compared with 51 historical controls who were desensitized but did not receive eculizumab. The incidence of acute AMR at 1 year was 7.7% in the eculizumab group compared with 41.2% in the historical control group. Graft and patient survival was excellent in both groups. Notably, screening kidney biopsies were normal, whereas patients received eculizumab, and the incidence of transplant glomerulopathy at 1 year was 6.7% in the eculizumab group but 36% in the control group. More recent data from the same group highlight that the incidence of transplant glomerulopathy was not different between the two groups.[23] However, it must be stressed that the duration of eculizumab therapy was not the same in all patients, as therapy duration was decided according to serial flow cross-matches. Patients with longer duration therapy exhibited the most positive flow cross-match. Eculizumab did not impact DSA levels. The conclusion of this seminal study was that eculizumab prevented the occurrence of acute AMR as long as it was administered. A randomized trial in living-kidney donor recipients is currently ongoing in which patients received eculizumab during a period of 3 months in one group and no eculizumab in the control group. All of these patients were desensitized according to local practice. The results of this trial will be very important because data on the prevention of acute AMR during the first 3 months following transplantation, the incidence of acute and chronic AMR afterward, and the incidence of chronic lesions of AMR in screening 1-year biopsies are critically needed. However, a recent press release about this study stated that the primary end point was not different between the two groups. It will of utmost importance to determine whether AMR lesions occur after drug administration is interrupted, which would suggest that eculizumab should be given for longer periods of time. Another study in deceased-donor kidney recipients is also ongoing without a control group. This study will provide useful data on drug efficacy in a different patient population. Studies are currently ongoing to treat acute

Table 2 | Current clinical trials of eculizumab and C1-esterase inhibitors in kidney transplantation

Eculizumab
- Prevention of delayed graft function (compared with placebo: NCT01756508, NCT01919346, NCT02134314, NCT01403389)
- Prevention of acute clinical antibody-mediated rejection:
  - In living donor kidney transplantation (NCT01399593): patients have been desensitized according to local practice (IVIg, plasma exchange) but without anti-CD20 and then randomized to receive either local practice treatment (IVIg, plasma exchange) or eculizumab for 9 weeks
  - In deceased donor kidney transplantation (NCT01567085): kidney transplant recipients with anti-HLA donor-specific antibodies (peak or day-0 serum >3000 MFI) have been given eculizumab for 9 weeks without any control group
- Treatment of acute antibody-mediated rejection (NCT01895127): a randomized open label trial comparing eculizumab with plasma exchanges and IVIg in the treatment of acute ABMR
- Treatment of subclinical antibody-mediated rejection (NCT02113891). Study withdrawn
- Treatment of chronic antibody-mediated rejection (NCT01327573): a randomized open label trial comparing eculizumab with regular immunosuppression
- Prevention of recurrence in:
  - C3 glomerulopathy (NCT01221181, NCT02093533): a single-arm study testing the efficacy of eculizumab to treat recurrence of dense deposit disease and C3 glomerulopathy
  - Antiphospholipid syndrome (NCT01029587): a phase 2 study to prevent thrombosis of the kidney transplant in patients with a catastrophic antiphospholipid antibody syndrome
- ABO-incompatible transplantation (NCT01095887): an open label trial aiming at preventing ABMR in ABO-incompatible living donor kidney transplant recipients

C1 esterase inhibitor
- Prevention of delayed graft function (NCT02134314)
- Use of human C1 esterase inhibitor to treat acute ABMR (NCT01147302)
- Safety and tolerability of Berinert to prevent rejection (NCT01134510)

Abbreviations: ABMR, antibody-mediated rejection; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin; MFI, mean fluorescent intensity.

clinical and subclinical ABMR, but only anecdotal reports are available.

Eculizumab has also been used in kidney transplantation to treat or prevent aHUS 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 by Zuber *et al.*[24] Twenty-one patients from an extensive literature search and a French national survey were studied. Hematological normalization was obtained in a group of 19 adults who were treated for a mean time of 30 days postrecurrence, and serum creatinine decreased from 295 ± 171 to 135 ± 69 μmol/l during the first 3 months posttreatment. Notably, greater renal function improvement was observed with earlier drug administration after recurrence. Eculizumab was used to prevent aHUS recurrence in nine children. One patient lost his transplant from artery thrombosis, but no recurrence was observed in all other cases, and renal function was excellent (71.6 ± 44.8 μmol/l) after a mean follow-up of 14.5 months. The main conclusions from the published experience in aHUS were that eculizumab is efficient for the treatment and prevention of recurrence after kidney transplantation. The earlier the treatment given, the better renal function recovers. Treatment tolerance is good, but the prevention of meningococcal infections is mandatory. Complement workup is not necessary to initiate treatment, but it should be performed for long-term management. Treatment duration still remains a matter of discussion.

In addition to these patients treated for posttransplant recurrence, two clinical trials demonstrated the efficacy and safety of eculizumab in adult aHUS patients with transplanted kidneys who were either resistant to plasma exchange/plasma infusion (PE/PI) (17 patients) (C08-002) or had chronic kidney disease on long-term PE/PI (20 patients) (C08-003).[19] The proportion of patients with complement mutations or anti-complementary FH antibodies was approximately 70% of patients with posttransplant HUS. 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. However, many patients did not reach full rescue of normal graft function, despite being in remission of hematological markers of tissue microarray under eculizumab. More than 50% of patients exhibited a serum creatinine >120 μmol/l at the last follow-up. Different mechanisms including brain-death–related injury, I/R injury, infections, the use of immunosuppressive drugs, and rejection may explain this result.[6] The option of prophylactic eculizumab treatment is likely the most suitable treatment for patients who are at a high risk for posttransplant recurrence.

Eculizumab has been administered to several kidney transplant recipients with recurrence of C3 glomerulopathy with inconstant efficacy,[25] antiphospholipid syndrome, and even the catastrophic form of this disease, and very promising results were reported.[26] Soluble CR1 re-establishes the regulation of the AP pathway and provides support for a limited trial to evaluate soluble CR1 as a treatment for dense deposit diseases and C3GN.[27] Because of the physiopathology of I/R in organ transplantation, it was very tempting to try to block complement activity. Trials are currently ongoing (Table 2) 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.

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 (Montgomery *et al.*, World Transplant Congress 2014, abstract 2252) or desensitize patients,[28]and a good safety profile and encouraging preliminary efficacy data are reported.

THE FUTURE: PROMISING COMPLEMENT INHIBITORS ARE IN THE PIPELINE

More than 20 complement therapeutics are currently in development.[29] 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 (mini FH, TT30) and CR1 (sCR1, TT10, APT070 or Mirococept), or inhibiting serine proteases (C1 inhibitor or anti-MASP2 and anti-OMS872). Therapeutic blockade of the anaphylatoxin effects using a C5a receptor (CD88) antagonist is challenging to modulate the inflammation.[30] Specific alternative therapeutics include the use of FH concentrate from human plasma or recombinant, which will be an appropriate choice for patients who present complete or partial FH deficiency.

DISCLOSURE

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