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# Eculizumab in kidney diseases

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**ABSTRACT**

The C5 inhibitor monoclonal antibody, eculizumab, has been approved for the treatment of atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH); however, the efficacy and safety of this drug in treating other complement-related renal diseases has not yet been elucidated. The high cost of eculizumab therapy and the rare adverse effects have created a paradox in conducting large clinical trials. Therefore, there is a need to increase clinicians' awareness of the available data on the efficacy/safety of this drug in treating renal diseases. Herein, we have reviewed the outcomes of the administration of eculizumab in aHUS, PNH, lupus erythematosus nephritis, C3 glomerulonephritis, IgA nephropathy, and antibody-mediated rejection (AMR) in highly sensitized patients. Initial findings suggest its efficacy in treating acute injuries but lower effectiveness in preventing chronic lesions. Besides, early diagnosis and timely initiation of eculizumab are of particular importance.

Review

*Implication for health policy/practice/research/medical education:*
Apart from the approved indications, eculizumab may help to treat complement-related kidney diseases. Eculizumab appears to be effective in treating acute injuries; however, it shows low efficacy in preventing chronic lesions. The high cost and low adverse effects of eculizumab are the main disadvantage and advantage of eculizumab therapy, respectively.

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## Introduction

In recent years, significant progress in developing monoclonal antibodies has brought new hopes for treating incurable diseases. The efficacy and specificity of monoclonal antibodies have been shown in managing many autoimmune, cancer, and infectious diseases and treating transplant rejection (1,2). A few antibodies have been used to treat particular kidney diseases, e.g., rituximab for membranous glomerulonephritis and daclizumab for transplant induction (3). Eculizumab, an inhibitor of the terminal complement system, has been considered in managing complement-related disorders affecting renal vasculature (4). In addition, eculizumab appears to be a relatively safe drug, as there are few reports of side effects, including increased risk of infection (e.g., meningococcal meningitis), hypertension, headache, and gastrointestinal complications associated with its administration (5).

Considering the potential of eculizumab in the treatment of many complement-related disorders such as lupus erythematosus, C3 glomerulopathy, IgA nephropathy, antibody-mediated rejection (AMR), atypical hemolytic uremic syndrome (aHUS), and paroxysmal nocturnal hemoglobinuria (PNH), in addition to the high cost of eculizumab therapy, there is a need to increase the awareness of the clinicians about the advantages and disadvantages of this drug in treating these ailments. In the present study, we have summarized the outcomes of the administration of eculizumab in patients afflicted with the aforementioned disorders.

## Eculizumab

Eculizumab (Alexion, Soliris) is a humanized monoclonal IgG2/4 that binds specifically to complement protein C5 with high affinity, preventing its cleavage into C5a and C5b fragments. It has already been approved for treating paroxysmal, nocturnal hemoglobinuria, aHUS, generalized myasthenia gravis (gMG), and neuromyelitis optica spectrum disorder (NMOSD). According to the

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increased risk of neisserial infections, the patients are suggested to be vaccinated against *Neisseria* meningitidis before treatment with eculizumab or receive prophylactic antibodies such as phenoxymethylpenicillin (6). Eculizumab is administered by intravenous infusion over 25–45 minutes, so the bioavailability is 100%. The half-life of eculizumab is estimated to be 272 ± 82 hours. Its distribution appears to be limited to the vascular space. Serum concentrations of eculizumab reach a steady state after approximately eight weeks. At a steady state, the eculizumab accumulation ratio is calculated to be 1.075, indicating minimal accumulation over time. Drug elimination mainly occurs via urine; only a small amount is excreted in bile (7).

## Atypical hemolytic uremic syndrome

Hemolytic uremic syndrome (HUS) is defined as an acute onset of renal impairment with increased serum levels of urea and creatinine, thrombocytopenia, and microangiopathic hemolytic anemia. It is classified into two groups: typical or shiga toxin-mediated HUS, including approximately 90% of cases, and aHUS, which may be familial or sporadic (8). Atypical HUS (aHUS) appears to be developed because of a dysregulation of the alternative complement pathway, as some mutations in the complement system genes have been demonstrated in the patients. For instance, factor H, factor I, factor B, membrane cofactor protein (CD46), and thrombomodulin (THBD) have been reported to be dysregulated in aHUS (9). Long-term complications of aHUS can lead to end-stage renal diseases (ESRDs); however, the outcome of transplantation is poor due to the recurrence of the disease.

Some studies demonstrate eculizumab's efficacy in controlling renal injuries in aHUS patients. For instance, two clinical phase II studies enrolling 17 and 20 aHUS patients with progressive, chronic kidney diseases (CKDs) showed promising results after 26 weeks of eculizumab administration. The extension phase, including 13 and 19 patients, was continued to 100 and 114 weeks, respectively. The results showed hematologic normalization, renal improvement, and thrombotic microangiopathy (TMA) event-free status in many patients at the time points of one year and two years. There were no cases of meningococcal infection in these trials, and none of the serious adverse events leading to death or discontinuation of the eculizumab could be related to this drug (10). Likewise, a 4-year prospective, observational study including 21 aHUS patients who received eculizumab for three months showed complete recovery of hematological TMA and considerable renal response in 10 patients, partial recovery in eight patients, and no recovery in three. Four of the 18 responsive patients experienced relapse after discontinuing the drug. One patient received a kidney transplant successfully during the follow-up period without the need for prophylactic eculizumab. Besides, this study reported a meningococcal infection and one hair loss as the adverse effects of eculizumab administration (11). Moreover, there was a report of better responses to eculizumab in aHUS patients compared to the C3 glomerulonephritis (C3GN); since, in aHUS patients, effective complement inhibition with a significant reduction of total complement activity (CH50), alternative pathway activity (APH50), C3d and sC5b-9 were observed. C3 glomerulonephritis patients presented increased C3d and consistently low C3 levels, reflecting ongoing complement activation and consumption of C3 protein (12).

In addition, eculizumab has been used as prophylaxis or treatment of disease recurrence in aHUS patients who underwent transplantation. For example, a 42-year-old woman with familial aHUS who presented a recurrence of the disease three years after the second renal transplantation was recovered temporarily by plasmaphereses. However, the patient's symptoms deteriorated promptly. After being vaccinated against meningococcal polysaccharide, eculizumab was started, which resulted in improved hematological signs and better renal function. Of note, the patient experienced two episodes of hemodialysis, transfusion, and deteriorated renal function due to delayed infusion of eculizumab; however, the situation ameliorated after receiving the next dose (13). Similarly, a 15-year-old male patient with aHUS and ESRD had two renal transplantations at 2.5 and 8 years of age; however, allograft dysfunction developed in both transplants leading to graft failure due to recurrent HUS. At 15 years of age, he received a third transplant from a deceased donor with pre-emptive plasmapheresis. Two months after transplantation, the patient developed severe allograft dysfunction and hypertension following an influenza infection. Renal allograft biopsy showed TMA. Thus, he received plasmapheresis followed by eculizumab therapy. Three weeks after salvage therapy, graft function returned to baseline, and allograft biopsies showed improvement in TMA. He receives eculizumab every two weeks with stable graft function 13 months after transplantation (14). Moreover, the CUREiHUS study has reported outcomes of administering eculizumab to patients with recurrent aHUS post-transplant. They included 15 patients, seven with early recurrence (median three months) and eight patients presenting late relapse (median 46 months). Treatment with eculizumab improved or stabilized glomerular filtration rate (GFR) in 14 patients. Discontinuation of therapy was successful in three patients. At the end of the follow-up (median 29 months), three patients lost their grafts, and six had GFR less than 30 (15).

Prophylactic eculizumab could also preserve the kidney allograft in aHUS patients who received it before or after transplantation (16-18). In a clinical trial, eculizumab (along with meningococcal vaccine) was given to 10 recipients out of 19 at the time of transplantation. None of these patients experienced aHUS recurrence

during the follow-up of approximately four years (range 6–237 months) months. The mean eGFR at the last follow-up was 59.5 mL/min/$m^2$, and no considerable infectious complications were reported (19). In a similar study, 38 patients received eculizumab at the time of transplantation, while 32 recipients did not. The results showed that death-censored graft survival was significantly higher in the prophylaxis group as it was 79%, 64%, and 61% (in three months, one year, and three years) in the controls compared to 100%, 97%, and 89% respectively in the prophylaxis group. However, one graft failed due to Neisseria meningitidis B bacteremia. The patient was not vaccinated against this serotype and did not receive prophylactic antibiotics (20). Another study compared the efficacy of eculizumab prophylaxis before and after transplantation. Eighty-eight patients received prophylactic eculizumab before, and 100 patients received it after transplantation. The latter group was diagnosed either before transplantation or after it. After five years of follow-up, they demonstrated higher rates of dialysis post-transplant in the patients diagnosed and received eculizumab after transplantation. Moreover, six months after the transplant, graft function in patients diagnosed and receiving eculizumab before the renal transplant was significantly better than in other groups (median eGFR 60.6 versus 31.5 and 9.6 mL/min/1.73 $m^2$). One meningococcal infection was reported, which was treated successfully, and three deaths occurred unrelated to the eculizumab. The findings of this study indicated the importance of early diagnosis of aHUS and prophylaxis pre-transplant (21). Similarly, a meta-analysis analyzing 18 studies, including 13 cohort studies and five case series consisting of 380 adult kidney transplant patients with aHUS who received eculizumab for prevention and treatment of post-transplant aHUS recurrence, demonstrated better outcomes in the prophylactic group. The results showed that the rate of TMA and graft loss in the prophylactic group was 6.3% and 5.5%, respectively, compared to the 22.5% allograft loss due to TMA in the patients receiving eculizumab post-transplant. These findings indicate the preference for the administration of eculizumab before or at the time of transplantation in aHUS patients (22).

The other important issue in the administration of eculizumab is the duration of treatment. Reports indicate an approximately 30% recurrence rate after discontinuation of eculizumab in aHUS patients. Therefore, treatment discontinuation should be done under close monitoring of the hematological and nephrological parameters such as hemoglobin, platelets, serum creatinine, and lactate dehydrogenase (LDH) at two and four weeks, then monthly for six months, and then every three or four months. In addition, risk stratification might be performed according to the high-risk mutations, such as specific variants in membrane cofactor protein (MCP) and complement factor H (CFH) (23).

## Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria is a rare form of hemolytic anemia caused by a genetic mutation, which results in glycolipid glycosylphosphatidylinositol (GPI) deficiency. Glycosylphosphatidylinositol is an anchor to hold many membrane proteins, including CD55 (decay accelerating factor) and CD59, which play a significant role in regulating the complement system's alternative pathway. In the absence of GPI, autonomous hydrolysis of C3 leads to excessive formation of membrane attack complex (MAC) on red blood cells, causing hemolysis, thrombosis, and end-organ damage (24). Kidneys might be affected by recurrent thrombosis resulting in a range of renal dysfunctions from acute reversible dysfunction to CKD requiring dialysis or organ replacement (25). Other possible mechanisms of kidney injury in PNH include hemoglobin toxicity to renal tubules, hypovolemia and renal ischemia, glomerular deposition of fibrin, and vasoconstriction due to pigment scavenging (26). Approximately 65% of the patients with PNH are affected by CKD (27,28). Considering the destructive role of C5 and MAC in the pathogenesis of PNH, some clinical trials have been conducted to evaluate the efficacy of complement inhibition in treating PNH patients (29). The initial attempts showed encouraging results as episodes of hemoglobinuria, mean LDH levels, and transfusion rates significantly decreased in the patients receiving eculizumab (30,31). Furthermore, the administration of eculizumab improved renal function in PNH patients with CKD. Indeed, it led to a reduction in proteinuria and a significant increase in GFR, which was more prominent in the patients with baseline CKD stages 1–2. In one study including 19 PNH patients with CKD, it was shown that 11 (69%) out of 16 patients with CKD stage 1–2 at baseline improved with eculizumab; while one (33%) out of the three patients with CKD stage 3–5 had significant improvement (28). In a similar study, after 18 months of treatment with eculizumab, a significant improvement of renal function was observed in CKD stages 1–2 (49/73 patients 67.1%), while the improvement rate in patients with CKD stages 3–4 was 8/35 (22.9%). Moreover, 21% of the PNH patients who demonstrated renal dysfunction or damage at baseline were no longer classified as such after 18 months of treatment (27).

## C3 glomerulonephritis

C3 glomerulonephritis (C3GN) is characterized by the accumulation of C3 or its metabolites in glomeruli without marked deposition of the early components of the classical pathway of complement activation and with minimal or no, immunoglobulin deposits. C3 glomerulonephritis is a prototypic complement-mediated kidney disease (32). Accordingly, eculizumab might be helpful in disease management, as some significant

improvement in renal function has been observed in C3GN patients with renal injury. For instance, a pediatric case with C3GN and nephrotic-range proteinuria that was refractory to treatment with rituximab, corticosteroids, and mycophenolate showed declined proteinuria and improvement of pathologic lesions after receiving eculizumab. However, disease signs relapsed by treatment interruption, resolving by drug reinitiation. Three years after eculizumab therapy, the patient have been treated with a maintenance dose of 1200 mg every two weeks without using other immunosuppressive agents (33). Furthermore, six patients with dense deposit disease (DDD), proteinuria >1 g/d, and/or acute kidney injury (AKI) were treated with eculizumab every other week for 12 months. After one year, two patients had significantly reduced serum creatinine, one showed reduced proteinuria, and one had stable creatinine and proteinuria despite histopathologic improvements. The patients presented normalized levels of soluble MAC associated with decreased amounts of creatinine and proteinuria (34). Additionally, when eculizumab was administered to seven patients with C3GN (five with C3 glomerulonephritis and two with DDD), four subjects showed significantly improved or stable renal function and proteinuria. Two patients showed a deteriorating condition, and one patient experienced recurrent C3GN post-transplant and showed a transient response but disease relapse after drug discontinuation. In responsive cases, disease improvement occurred between two weeks and six months after therapy initiation (35). Additionally, there are other reports of renal function recovery 2–3.5 months after initiation of eculizumab in dialysis-dependent patients with C3 glomerulonephritis (36).

Eculizumab has shown efficacy in the control of rapidly progressive C3GN, which was refractory to conventional immunosuppressive drugs and plasmapheresis. Three patients with increased levels of creatinine (two patients with a history of nephrotic syndrome) were treated with eculizumab. During the first week of treatment, the patients showed improved GFR associated with reduced C5b-9 deposition and remission of nephrotic proteinuria (37). In addition, a 29-year-old woman with DDD presented with deterioration of graft function and increased proteinuria four weeks after renal transplantation and disease recurrence showed poor response to corticosteroid, rituximab, and plasmapheresis; therefore, eculizumab rescue therapy was started that after 13 weeks resulted in a significant decrease in serum creatinine and urine albumin to creatinine ratio (ACR) (38). On the other hand, a patient with DDD and allograft recurrence of C3GN who was receiving eculizumab every other week for one year showed an initial reduction of the soluble MAC levels and decreased proteinuria; however, at 12 months, proteinuria increased to pretreatment levels and despite stable serum creatinine, allograft biopsies showed disease progression (39).

## Lupus nephritis

Systemic lupus erythematosus (SLE) is an autoimmune disease with anti-double stranded DNA (dsDNA) antibodies and dysregulated complement activity. Secondary TMA is a severe complication of SLE (40). Eculizumab has not yet been approved for treating SLE; however, there are some reports of using eculizumab as rescue therapy in severe resistant lupus nephritis. For example, a 14-year-old female case of SLE nephritis presented with proteinuria, high protein/creatinine ratio, low albumin levels, and diffuse proliferative glomerulonephritis in renal biopsy was under treatment with cyclophosphamide, rituximab, and mycophenolate mofetil; however, after 15 months renal function decreased and an active class IV lupus nephropathy was observed in the biopsy. Tacrolimus was administered, but the renal function deteriorated. Therefore, eculizumab was started resulting in rapid improvement of renal function. Eighteen months later, despite pathological evidence of nephropathy, C9 was undetectable and inflammatory marker CD68 was significantly reduced in biopsy (41). Similarly, a 4-year-old girl with diffuse proliferative lupus nephritis unresponsive to prednisone, plasma exchanges, and cyclosporine showed prompt remission of vasculitis, proteinuria, and hematuria, with normalization of renal function after receiving eculizumab. However, two attempts to withdraw eculizumab led to severe relapses but were rescued by reinitiation of treatment. The patient has been treated with eculizumab for over 17 months without relevant side effects (42). A 24-year-old female case of SLE with anemia, thrombocytopenia, and AKI showed class III-V lupus nephritis indicative of TMA. After unresponsiveness to cyclophosphamide, plasmapheresis, and high-dose methylprednisolone, she received eculizumab. After two weeks, the patient's creatinine level decreased significantly, and her GFR increased. After six months of eculizumab treatment, the patient had a creatinine level of 1.6 mg/dL, GFR 47 mL/min/1.73 $m^2$, ACR 1.6 mg/mg, and regular C3 and C4 levels (43). Further, a 55-year-old woman known for SLE, biopsy-proven class IV lupus nephritis, and membranoproliferative glomerulonephritis with dominant C3, after suboptimal response to azathioprine mycophenolate mofetil and rituximab, showed significant improvement with eculizumab therapy. The patient's proteinuria reduced from 5.5 g to 1.4 g, and serum albumin raised from 2.5 mg/dL to 4.0 mg/dL. The serum creatinine levels were normal and stable during the follow-up period (44). Likewise, a 27-year-old woman with SLE and ESRD due to fulminant TMA and positive antiphospholipid and anti-nucleosome antibodies receiving living-related kidney transplantation showed increased creatinine and TMA recurrence levels on the sixth-day biopsy. The patient underwent plasma exchange, but the disease

deteriorated, and dialysis was started. Nonetheless, after the initiation of eculizumab treatment, renal function improved dramatically, and three months post-transplant, serum creatinine was 100 μmol/L, without pathologic proteinuria (45). Finally, a case series review analyzing the data of nine patients with SLE and/or antiphospholipid syndrome showed a 25% improvement in GFR and a 43% reduction of proteinuria after 4 weeks of treatment with eculizumab. Moreover, two out of three patients who were under hemodialysis became dialysis-free (46).

### IgA nephropathy

Immunoglobulin A nephropathy (IgAN) is a chronic glomerulonephritis with excessive glomerular deposition of IgA1, C3, and C5b-9, which may lead to renal failure (47). Therefore, complement activation plays a substantial role in the pathogenesis of the disease, and complement inhibition might help manage the patients. Accordingly, a few complicated cases of IgAN have been treated with eculizumab. For example, a 16-year-old male diagnosed with IgA nephropathy presented elevated creatinine levels, decreased plasma albumin, hematuria, and proteinuria with elevated urinary ACR under prednisolone and MMF therapy. By deterioration of disease and prominent C5b-9 deposition indicating rapid progression of renal failure, eculizumab was started. The patient showed an initial improvement in creatinine, but it elevated again; nevertheless, proteinuria attenuated and remained low. Six weeks after quitting eculizumab therapy, renal function was impaired. The patient received an additional dose of eculizumab but renal function was not improved, and a biopsy revealed chronic progressive damage. A remarkable creatinine rise occurred four weeks later, and peritoneal dialysis started for the patient (48). Eculizumab therapy showed partial creatinine reduction in another 16-year-old male IgAN patient who was refractory to the conventional therapy; however, proteinuria showed no considerable reduction, and histologic evaluation demonstrated considerable chronic lesions such as interstitial fibrosis/tubular atrophy, indicating disease progression (49).

Eculizumab has been used for treating the recurrence of IgAN after kidney transplantation. A 28-year-old male patient with ESRD secondary to IgAN who underwent kidney transplantation showed acute graft failure due to disease recurrence two months post-transplant. He received cyclophosphamide, tacrolimus, and steroid treatment, but graft function showed no recovery. Following severe impairment of renal function, hemodialysis was initiated, and eculizumab was administered, but despite receiving four doses of eculizumab (a cumulative dose of 1800mg), no considerable response was observed (50). On the other hand, a 50-year-old female with IgA nephropathy and ESRD secondary who received a kidney transplant from a deceased donor showed good early responses to eculizumab therapy. The patient developed acute graft dysfunction five months after transplantation, with severe AMR and TMA, unresponsive to the conventional immunosuppressive regimen. Eventually, the patient was treated with three doses of eculizumab, which significantly improved TMA and stabilized graft function. However, follow-up biopsies demonstrated ongoing signs of rejection and chronic lesions (51).

### Antibody-mediated rejection in highly sensitized patients

Apart from the abovementioned studies that have administered eculizumab for treating the recurrence of underlying diseases post-transplant, there have been attempts to manage refractory forms of AMR (52). In most cases, AMR could be resolved with conventional therapies, including plasmapheresis, intravenous immunoglobulin (IVIG), and anti-CD20 therapy. However, in complicated cases, particularly in sensitized patients, high amounts of antibodies bind to the endothelium of the allograft and activate the complement system cascade through classic and lectin pathways (53).

One of the first AMR cases which were reported to be successfully treated with eculizumab was a 34-year-old female recipient of a simultaneous pancreas/kidney transplant who developed AMR and de novo TMA seven days post-transplant. The patient responded partially to treatment with daily plasma exchange and IVIG, but hemodialysis started because of the worsening condition. Then, the patient received a single dose of eculizumab, resulting in normalized platelet count and serum LDH, improved renal function, and quitting hemodialysis within two days (54). The other case was a 43-year-old male with ESRD due to type I diabetes who received an ABO-incompatible (A1 to O) kidney/pancreas transplant from a deceased male donor after plasma exchange. The patient showed elevated levels of isohemagglutinins and distinctive peritubular C4d deposition on day six of transplantation. Since rituximab and basiliximab had been used as induction therapy, eculizumab 600 mg was administered on days 10 and 14 post-transplant, significantly improving allograft function. Six-month follow-up showed plasma creatinine of 77 μmol/L, GFR of 106 ml/min/1.73 $m^2$, HbA1c of 37 mmol/mol, and normal glucose tolerance (55). Another complicated case of AMR treated by eculizumab was a 20-year-old male with previous kidney transplantation and a history of several blood transfusions due to hematologic malignancy. The patient received a living, related kidney after desensitization by plasmapheresis/IVIG; however, the patient developed AMR a few days post-transplant with extensive granular deposition of C5b-9. Regarding his poor response to conventional treatments, on day 10, eculizumab was added to rituximab/high-dose IVIG therapy, which caused a significant decrease in MAC deposition and

resolution of the AMR (56). Furthermore, a 43-year-old female patient with ESRD and 100% panel reactive antibody (PRA) that received desensitization therapy with rituximab, bortezomib, IVIG, and plasmapheresis before transplantation developed thrombotic complications and diffuse C4d staining post-transplant. With the diagnosis of severe AMR, eculizumab was initiated at 1200 mg on day 4, followed by weekly doses of 600 mg (four weeks) and maintenance doses of 1200 mg on days 40, 52, and 64. The renal function was restored gradually, and a 6-month follow-up demonstrated normal creatinine and undetectable donor-specific antibodies (DSA) titers (57). Similarly, a highly sensitized 13-year-old female with ESRD secondary to reflux nephropathy that underwent transplantation after emotional desensitization developed refractory AMR with TMA at the end of the first week. Therefore, eculizumab rescue therapy was initiated, which resulted in a dramatic improvement in creatinine levels and platelet count within six days. Interestingly, the patient was revealed to be complement factor H-related protein 3/1 (CFHR3/1)-deficient, a protein that might contribute to the development of severe AMR associated with TMA (58). Furthermore, one study comparing two groups of sensitized patients who received either plasma exchange or plasma exchange plus eculizumab demonstrated that after two years of follow-up, the incidence of AMR was significantly lower in the eculizumab group than in controls (6.7% versus 43.8%); however, death-censored allograft survival was comparable between groups. Moreover, the two groups developed chronic antibody-mediated rejection (CAMR) at a similar rate, suggesting that despite reducing AMR rates, eculizumab might not prevent CAMR in sensitized recipients (59). Similarly, the results of an observational retrospective study comparing 30 eculizumab-treated, positive crossmatch kidney transplant recipients with 48 positive crossmatch and 78 negative crossmatch controls in approximately seven years demonstrated similar death-censored allograft survival rates between positive crossmatch groups but lower than the control patients. Although DSA levels were decreased in eculizumab-treated patients, the rate of chronic rejection did not reduce compared to non-treated recipients (60). On the other hand, the results of the phase 2 randomized trial, including 102 sensitized patients, half of them under the standard of care (SOC) and the other receiving SOC + eculizumab (before graft reperfusion and for nine weeks post-transplant), showed no significant differences in patient or graft survival between treatment groups. Indeed, a comparable incidence of acute AMR (grade II or III) was observed between the eculizumab and SOC groups. However, the rate of grade I AMR was 11.8% in the eculizumab and 29.4% in the SOC group, respectively (61). Finally, a pilot study hypothesizing that de novo DSAs cause complement-dependent endothelial cell injury in kidney transplants assessed the expression of endothelial cell–associated transcripts (ENDATs) in renal transplant recipients. Fifteen patients with DSA and deteriorating allograft function were enrolled. Ten patients received six months of eculizumab followed by six months of observation whereas five recipients were only observed. Graft function in the treatment group was improved compared to the control; however, biopsies demonstrated elevated ENDATs in most participants and were comparable between the two groups (62).

## Discussion

Eculizumab, a terminal complement inhibitor, has been approved to treat certain complement-dependent disorders; however, it appears to help manage other complements–related renal injuries such as C3 glomerulonephritis, IgA nephropathy, SLE nephritis, and antibody-mediated transplant rejection. Case reports and clinical trials have provided evidence of eculizumab's efficacy in improving renal function in the aforementioned disease but to different degrees. For instance, one study demonstrated less satisfying response to eculizumab by C3GN patients compared to the aHUS patients (12). Indeed, C3GN patients may benefit from complement inhibition, but the response to eculizumab is heterogeneous. The researchers suggest determining genetic and functional abnormalities of the complement system to predict the response of these patients to treatment. For example, elevated SMAC levels could predict better response than normal levels. The time and duration of treatment are essential because the results suggest effective prevention if eculizumab therapy is initiated early and remains continuous, which might need further investigations regarding the high cost of this drug (35-37). Furthermore, C5 inhibition has shown promising results in SLE patients with severe lupus nephritis. Eculizumab may be a potential treatment option for critically ill patients with secondary TMA due to SLE and/or APS being unresponsive to conventional therapy (43,46). The few studies about the efficacy of eculizumab in treating IgAN indicate that complement inhibition might benefit patients, but the development of chronic lesions may be independent of complement activation. If eculizumab is administered for post-transplant recurrence, it is suggested to be used early after diagnosis to be effective (49-51).

Transplant candidates with positive crossmatch, high PRA percentages, and ABO incompatible donors are at high risk of graft failure. Eculizumab has shown encouraging results in cases severe AMR and TMA were observed in these patients, and standard care treatments have failed to ameliorate the situation. Similar to previous disorders, early administration of eculizumab before the requirement of hemodialysis is critical. Moreover, some evidence indicates undiagnosed genetic mutations of complement regulatory proteins in severe forms of AMR in patients that present a good response to eculizumab treatment. Pre- or post-transplant genetic screening considering such mutations might be helpful in the

prevention and effective treatment of AMR (59-61).

Finally, according to the high specificity of eculizumab, there are few adverse effects reported relevant to the administration of this drug. The most prominent adverse effect is neisserial meningitis, which pre-treatment vaccination could efficiently prevent. Some studies have used prophylactic antibiotics for infection prevention. General side effects such as headache, bone pain, vomiting, and skin rash are not prevalent and could be managed by simple treatments. Besides, no death reports have been recorded in relation to eculizumab. These data suggest that eculizumab is a safe drug for treating poor prognosis complement-related renal diseases. Nonetheless, the high cost of this drug and the long-term need for treatment in chronic disorders might be a considerable disadvantage.

## Conclusion

Taken together, eculizumab is a potential treatment option for complicated cases of complement-related renal diseases. Its efficacy in the control of acute injuries is more than in chronic lesions, and in patients with genetic mutation of complement proteins is more significant than in typical cases. Eculizumab is costly but almost safe; nonetheless, more investigations are required to clarify the pros and cons of its administration in kidney diseases.

## Authors' contribution

**Conceptualization:** Fatemeh Pour-Reza-Gholi.
**Writing-original draft:** Fatemeh Pour-Reza-Gholi.
**Writing-review and editing:** Sara Assadiasl.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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