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Review Article

Eculizumab in Pediatric Kidney Disorders: A Review

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ABSTRACT

Eculizumab is a humanized monoclonal antibody targeting the C5 (complement 5) member of complement proteins and inhibiting its cleavage to C5a and C5b. Eculizumab has been proven to be effective in a wide array of nephrologic, neurologic, and hematologic pediatric disorders. Kidney disorders, particularly those with immune-mediated pathomechanism, are the most common indications of eculizumab, including atypical hemolytic uremic syndrome (aHUS), hemolytic uremic syndrome (HUS), membranoproliferative glomerulonephritis (MPGN), immunoglobulin A (IgA) nephropathy, hematopoietic stem cell transplant-associated thrombotic microangiopathy, and less commonly post-infectious glomerulonephritis and diffuse proliferative lupus nephritis. In this review, we aimed to summarize the current evidence on approved and off-label applications of eculizumab and their specific considerations in pediatric kidney disorders.

Keywords: Eculizumab, Complement C5, Complement, Kidney, Chil

Introduction

Eculizumab is a humanized immunoglobulin G (IgG)2/4 monoclonal antibody targeting the complement 5 (C5) member of complement proteins inhibiting its cleavage to C5a and C5b [1, 2]. Eculizumab is accepted as one of the treatment strategies for the overactivation of the complement system [2, 3]. The safety and effectiveness of eculizumab in immune-related disorders of the kidney is approved by the US Food and Drug Administration (FDA) for paroxysmal nocturnal hemoglobinuria (PNH) in adults and atypical hemolytic uremic syndrome (aHUS) in both adult and pediatric patients with the appropriate dosing [4]. In addition, multiple approved off-label indications for other dysregulations of the immune system are noted in daily practice and the literature [3, 5-7]. In this review, we aim to summarize the current evidence on approved and off-label applications of eculizumab in pediatric kidney disorders.

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History of eculizumab

The primary evidence of the effectiveness of humanized anti-C5antibodies in inhibiting and ameliorating human inflammatory disease dates back to the 1990s [8-10]. Over the next decade, increasing evidence supported the effectiveness of anti-C5 antibodies, registered under the name of Soliris (Eculizumab) by Alexion pharmaceuticals, which received its first FDA approval for the first-line treatment of PNH in adults in 2007 [11]. Four years later, eculizumab received its second FDA approval for safe and effective use in all patients with aHUS [12]. Eculizumab also received FDA approval for generalized myasthenia gravis and neuromyelitis optica spectrum disorder in 2017 and 2019, respectively [13, 14]. In the next section, we will review the current evidence about the role of eculizumab in the management of immune-mediated renal disorders and their specific considerations.

Pharmacodynamic and pharmacokinetic characteristics

Eculizumab is a humanized monoclonal antibody that can bind one or two C5 molecules and prevent the cleavage of C5 into C5a and C5b, resulting in the formation of C5b-C9, Fb factor b, membrane attack complex (MAC) membrane attack complex, and Mannan-binding lectin (MBL) with mannose-binding lectin (Figure 1) [15].

According to current evidence, eculizumab is distributed in a two-compartment pattern (including intravascular space and extracellular matrix) and eliminated by the first-order metabolism. Some variations, mostly time-variant or body weight-dependent are also reported [1]. As well, studies are investigating the effects of plasmapheresis, hemodialysis, and plasma exchange on its kinetics [1, 16].

Growing evidence addresses inter-personal variations in eculizumab concentration in patients with PNH and aHUS, emphasizing the importance of individualized dose adjustment [17-21]. However, according to the current literature and in vitro studies, a steady serum concentration between 99-700 mg/L is effective for complete complement blockage [21].

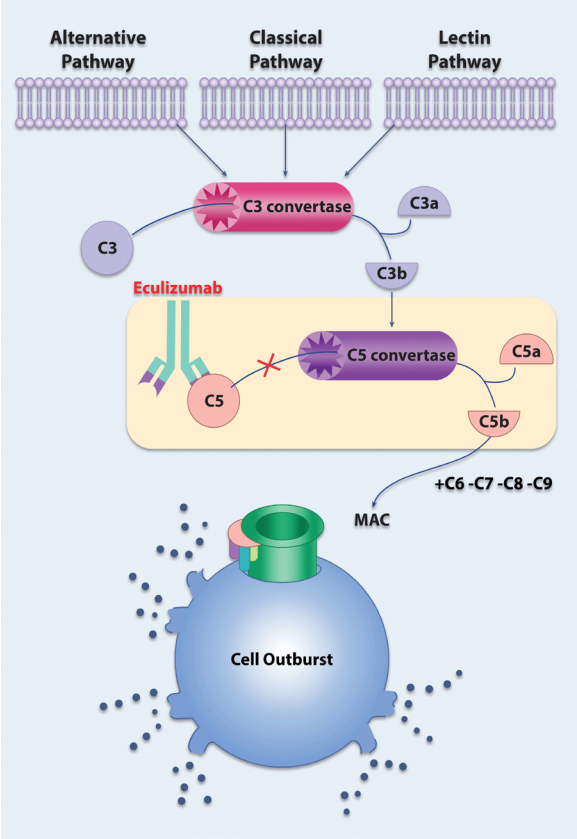

Figure 1. Eculizumab mechanism of action

Eculizumab is a monoclonal antibody that prevents the cleavage of C5 into C5a and C5b, thereby blocking the complement pathway. Abbreviations: MAC, membrane attack complex.

Indications

Atypical hemolytic uremic syndrome (aHUS)

Hemolytic uremic syndrome (HUS) occurs when the small blood vessels of the kidney are damaged and inflamed, leading to the formation of clots and kidney failure. The atypical form of HUS is a rare disease caused by an overactive complement. aHUS has non-specific symptoms that mostly include paleness, nausea/vomiting, fatigue, drowsiness, hypertension, and swelling.

Fakhouri et al. studied the length of eculizumab treatment in 55 patients with the aHUS (including twenty-eight patients with rare variants in complement genes). They observed that discontinuation of eculizumab increased soluble complement (sc)5b-9. While 13 patients had to continue eculizumab treatment, 11 patients gained normal renal function, of which 2 worsened and one progressed to end-stage renal disease [22].

A cohort study was performed by Muff-Luett et al. based on biomarkers of patients under 25 years of age who were treated with eculizumab. Among 152 patients studied, eculizumab was used "off-label" in 44% of cases and most patients had aHUS (47.4%) [23].

Tschumi et al. reported a case of aHUS. The patient was a 9-year-old girl with a factor H mutation who was allergic to plasma therapy and was treated with eculizumab every two weeks. The patient did not show any symptoms for more than 2 years [17].

Matrat et al. reported two cases of aHUS. The patients were two children with aHUS who had anti-cerebrospinal fluid (CSF) antibodies. Eculizumab therapy and MMF were used to treat aHUS and they experienced no symptoms for 3 years. In conclusion, eculizumab and MMF were effective in treating aHUS dependent on anti-CSF antibodies [18].

Özçakaret al. conducted a study on 12 children with aHUS. These children received a kidney transplant. Eight of them had received eculizumab, of which 7 had no recurrence of aHUS, and only one patient who started eculizumab therapy the day before transplantation had a recurrence of aHUS [24]. Menne et al. studied 93 patients with aHUS who received at least one dose of eculizumab. Forty-two patients discontinued eculizumab and another 21 resumed eculizumab. Patients who relapsed were clinically similar to patients who continued eculizumab therapy but had more genetic abnormalities. During the 6-year study, none of the patients showed symptoms of aHUS. Three definitive meningococcal infections related to eculizumab were reported and resolved with treatment [25]. Lilian Monteiro Pereira Palma et al. studied 34 Brazilian aHUS patients, 17 of whom were children. Among the patients, 31 patients received eculizumab. Although eculizumab was started later in adults, it was effective in improving patients, and most patients stopped dialysis. Discontinuation of eculizumab was associated with a 30% recurrence of aHUS [26].

Shuichi Ito et al. studied 27 children with aHUS in Japan with a median diagnosis age of 4 years. On average, treatment was started two days after the diagnosis of eculizumab therapy. They observed that in 75% of patients, complete TMA response, platelet normalization, and estimated glomerular filtration rate (eGFR) improved. And the result was that eculizumab therapy is effective for Japanese aHUS patients [27].

Rondeau et al. studied 1,321 aHUS patients, of whom 479 were pediatric patients and 456 were never treated. This large, global 5-year study concluded that no new safety concern for aHUS patients exists, whether children or adults treated with eculizumab [28].

Hemolytic uremic syndrome (HUS)

HUS is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. HUS is usually caused by Shiga toxin-producing Escherichia coli (STEC).

Symptoms include vomiting, bloody diarrhea, stomach pain, fever, chill, and headache. Percheron et al. studied 33 French children with severe STEC-HUS, 20 of whom had neurological involvement and 8 children had both neurological and cardiac involvement. Among 28 patients with neurological disorders, 19 patients showed optimal neurological outcomes after receiving eculizumab and 17 patients showed improvement after the first injection of eculizumab. It was concluded that eculizumab therapy is effective in improving STEC-HUS patients, especially those with neurological involvement [29]. This result was confirmed by the case report published by Jacob H Umscheid et al. which described a 3-year-old boy with STEC-HUS who had severe neurological involvement in addition to acute renal failure and was efficiently treated by eculizumab [30].

Kelen et al. reported the case of a 35-week-old child with low hemoglobin, renal failure, macroscopic hematuria, thrombocytopenia, and suspected HUS. After receiving a dose of eculizumab, renal function improved. It was

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Table 1. Summary of eculizumab application in kidney disorders

Condition	Clinical Outcome	Side Effects and Special Notes
aHUS [22, 27, 58-61]	Amelioration of inflammatory state, improved renal function (BP, GFR, proteinuria)	- Effective and safe treatment strategy
HUS [16, 62-71]	Amelioration of inflammatory state, improved renal function (BP, GFR, proteinuria), prevention of seizure recurrence	- Intradialytic administration of the eculizumab does not affect its kinetics. - Prevention of seizure recurrence, accompanied by a dramatic improvement in neurological state after the first dose - Effective and safe treatment strategy
MPGN [34-40]	Improved renal function (proteinuria, GFR)	-
IgAN [42]	Improved renal function (proteinuria, GFR)	-
TA-TMA [72, 73]	Improved renal function (BP, GFR, proteinuria)	- Effective and safe treatment strategy - Without the increased risk of infection in presence of adequate vaccination and antibiotic prophylaxis
Post-infection GN [28, 50]	Improved signs and symptoms of the nephritic syndrome	- Restore renal function and appropriate urine output leading to discontinuation of hemodialysis
DPLN [24]	Improved signs and symptoms of the nephritic syndrome	- Recurrence of nephropathy after discontinuation

HUS: hemolytic uremic syndrome; aHUS: atypical HUS; MPG: membranoproliferative glomerulonephritis; IgAN: immunoglobulin A nephropathy; TA-TMA: transplant-associated thrombotic microangiopathy; GN: glomerulonephritis; DPLN: diffuse proliferative lupus nephritis; GFR: glomerular filtration rate; BP: blood pressure.

concluded that infants with hemolytic anemia, thrombocytopenia, and renal failure suspected of HUS can benefit from first-line treatment with eculizumab [31].

Mahat et identified 16 reports of the use of eculizumab in the treatment of severe STEC-HUS with neurological or multiorgan dysfunction resulting in improved clinical symptoms after eculizumab therapy [32].

Weber et al. reported a case of a 13-year-old female with STEC-HUS associated with neurological involvement, seizures, altered mental status, and renal failure. Renal symptoms, seizures, and altered mental status improved after receiving two doses of eculizumab when used in parallel with hemodialysis [16].

Membranoproliferative glomerulonephritis (MPGN)

MPGN is an uncommon pattern of glomerular injury that has three types I, II, and III. Hypocomplementemia is observed in all three types, but the mechanisms of complement activation are different. Various forms of treatment are available with different efficiencies, with long-term steroid therapy effective in children with nephrotic-range proteinuria [33].

Based on immunofluorescence findings, MPGN has two types, such as complement-mediated C3 glomerulopathy (C3G), and immune complex-mediated MPGN (IC-MPGN). Currently used therapies, such as corticosteroids and immunosuppressants, are often ineffective in primary C3G and IC-MPGN. Eculizumab has occasionally been prescribed in single cases. However, only a few patients have been successfully cured [34]. In an article by Alfakeeh et al. in 2017, the first case of IC-MPGN with aHUS was successfully treated with eculizumab [35].

C3 Glomerulopathy (including recurrent C3 Glomerulonephritis, dense deposit disease [MPGN type II], complement factor H related 5 [CFHR5] nephropathy) are rare glomerular disease characterized by complement dysregulation occurring in the fluid phase and the glomerular microenvironment. Dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) are two major subgroups of C3 glomerulopathy with overlapping clinical and pathological features. Currently, no disease-specific treatments are available for DDD and C3 glomerulonephritis (C3GN), although immunosuppressives and terminal complement pathway blockers are prescribed in some patients [36]. In an article conducted by Holle et al. three patients received eculizumab and it was concluded that eculizumab can be a treatment option for C3G [37]. In an article by conducted Lebreton et al. the efficacy of eculizumab was illustrated in four patients. In three patients eculizumab normalized proteinuria, while in the fourth patient, the first eculizumab therapy had no

effect; however, after withdrawal and re-introduction of the eculizumab, proteinuria decreased moderately [38].

In an article conducted by Tran et al. a pediatric patient with DDD failed to respond to cyclophosphamide, corticosteroids, and plasma exchange but eculizumab therapy resulted in significant improvement in proteinuria and renal function, allowing discontinuation of hemodialysis [39]. In another article conducted by Vivarelli et al. 11 patients with different forms of C3G were successfully treated with eculizumab [40].

Immunoglobulin A (IgA) nephropathy

IgA nephropathy (IgAN) is the most common primary glomerulonephritis leading to renal failure. The exact pathogenesis of IgAN is not completely known. Patients have a wide range of signs and symptoms, from asymptomatic microscopic hematuria to macroscopic hematuria. Currently, no disease-specific treatments are available and patients are managed by maintaining renal function and controlling blood pressure [41]. In an article conducted by Rosenbladet al. an adolescent with rapidly progressive IgA nephropathy was treated with eculizumab (anti-C5) for 3 months in an attempt to rescue renal function and the patient had clinical improvement with stabilization of the glomerular filtration rate and reduced proteinuria. In this article, it was mentioned that the early beginning of eculizumab in patients with progressive IgAN may have a beneficial effect by blocking complement-mediated renal inflammation [42].

Hematopoietic stem cell transplant-associated thrombotic microangiopathy

Transplant-associated thrombotic microangiopathy (TA-TMA) is a disorder associated with renal disorder, hemolysis, and thrombocytopenia [29]. Sakamoto, Kenichi et al. reported a boy who had TA-TMA. To find out whether the complement is active in the patient, they used a staining technique. At last, they concluded that eculizumab can be effective to treat the child [43]. Another study checked a group of children with TA-TMA and reported that eculizumab cannot completely recover all patients [32].

TMA is a disease with thrombocytopenia and vascular damage. As a complication of systemic lupus erythematosus (SLE), TMA does not respond to usual treatments in many cases. But eculizumab may be a choice for this disease [44]. In a study, systemic lupus erythematosus (SLE) patients who received eculizumab had a remarkable resolution of TMA [45].

Vissing, Andrew et al. reported a boy with TMA secondary to pancreatitis. He had different manifestations, including vomiting, and abdominal and circulatory disruptions. With a suspected aHUS diagnosis, they aimed to use eculizumab. However, before using eculizumab, the patient's condition improved with other treatments. They concluded that no reliable evidence is available for the use of eculizumab in TMA [46].

Vaisbich, Maria Helena et al. reported a baby who had cobalamin deficiency, and they assumed that the baby had aHUS. They used eculizumab but it was not efficient. At last, they found out that methionine synthase deficiency (MSD) was problematic and eculizumab was not a good therapy for TMA-associated MSD [47].

In another case report, in a girl with SPA, TMA appeared after gene replacement therapy. In this case, Eculizumab is a good treatment to prevent the progression of renal disorders [48].

Post-infectious glomerulonephritis (PIGN)

Post-infectious glomerulonephritis (PIGN) can significantly induce acute glomerulonephritis in children [49]. Activation of complement has an obvious effect on Post-infectious glomerulonephritis (PIGN) [50]. High blood pressure, edema, blood in the urine, and nephrotic-range proteinuria are the most common symptoms of glomerulonephritis [25]. The treatment of a child who had post-infectious glomerulonephritis using eculizumab is reported. After the first administration of eculizumab, renal function improved and the patient no longer needed hemodialysis [50]. Two other children were examined with low C3 levels and acute post-infectious glomerulonephritis, one with anuria and the other with oliguria. Both were successfully treated with eculizumab [28].

Diffuse proliferative lupus nephritis

Diffuse proliferative lupus nephritis (DPLN) is the most prevalent type of lupus nephritis [51]. Swelling of the legs, hypertension, and blood in the urine are among lupus nephritis symptoms. Renal disruption and nephrotic syndrome show that DPLN is a progressive disorder [52]. Coppoet al. reported improvement of nephropathy in a child with DPLN receiving eculizumab but discontinuation of eculizumab resulted in relapse [23].

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Other non-renal indications

Myasthenia gravis

Myasthenia gravis (MG) is an autoimmune disease caused by acetylcholine receptor antibodies (AChR-Ab), with the involvement of cellular immunity and the complement system. Destruction of the acetylcholine receptor (AChR) on the postsynaptic membrane leads to insufficient potential at the end plate, resulting in impaired synaptic transmission at the neuromuscular junction and muscle weakness. The inhibition of the complement system in MG has been shown to prevent disease induction in patients with MG and reverse its progression [53].

MG patients resistant to conventional therapy or those who experience significant side effects after treatment with corticosteroids and at least two other immunosuppressive agents may benefit from novel treatments. According to the latest guidelines issued by the British Association of Neurologists and the German Neurological Society, eculizumab is a treatment for patients with severe and refractory MG [54, 55]. However, not enough long-term data are available to evaluate safety and efficacy.

Paroxysmal nocturnal hemoglobinuria (PNH)

PNH is hemolytic anemia caused by the clonal expansion of hematopoietic stem cells that have somatic mutations in the X-linked phosphatidylinositol glycan class A (PIG-A) gene. Intravascular hemolysis is a crucial feature of PNH and results from the absence of complement regulatory protein CD59, which is responsible for the formation of terminal complement complexes on the cell surface and preventing erythrocyte lysis and platelet activation [56]. Patients with PNH require frequent transfusions of packed cells to sustain hemoglobin levels, which remarkably decreases the patient's quality of life. Peter Hillmen et al. in 2006 reported that eculizumab is effective in PNH and can reduce the rate of transfusion by 73% [57].

Conclusion

Eculizumab is a humanized anti-C5 antibody that can ameliorate the complement over-activation via inhibition of the cleavage of C5 to C5a and C5b. As well as its approved application in aHUS, several pieces of evidence support its effectiveness in the clinical improvement of HUS, MPGN, IgAN, TA-TMA, post-infection GN, and DPLN in pediatric patients (Table 1). Personalized dose titration has been accompanied by the best treatment outcomes.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to the preparation of this article.

Conflict of interest

The authors declared no conflict of interest.

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