



Pharmacology, Pharmacokinetics and Pharmacodynamics of Eculizumab, and Possibilities for an Individualized Approach to Eculizumab

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Published online: 13 February 2019
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Abstract

Eculizumab is the first drug approved for the treatment of complement-mediated diseases, and current dosage schedules result in large interindividual drug concentrations. This review provides insight into the pharmacokinetic and pharmacodynamic properties of eculizumab, both for reported on-label (paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, generalized myasthenia gravis) and off-label (hematopoietic stem cell transplantation-associated thrombotic microangiopathy) indications. Furthermore, we discuss the potential of therapeutic drug monitoring to individualize treatment and reduce costs.

Key Points

To assess the optimal treatment scheme and minimize unnecessary use of the highly expensive orphan drug eculizumab, therapeutic drug monitoring should be performed.

Treatment algorithms, based on serum eculizumab levels and total complement activity (CH50), should be developed to guide individual dosing regimens.

1 Introduction

With orphan drug status in 2003 and approval in 2007, eculizumab (Soliris[®]) was the first drug targeting the complement system, specifically complement component C5 [1–3]. Since the approval of eculizumab, many trials have been conducted and various drugs targeting different proteins of the complement system are in the pipeline [4]. Until now, marketing authorization for eculizumab has been obtained for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), and refractory generalized myasthenia gravis (gMG) [1, 5, 6]. Noteworthy is the off-label use of eculizumab as a broad spectrum of other diseases (Table 1) [7].

Like other orphan drugs, costs as high as €500,000 per patient per year are associated with eculizumab therapy [8]. Consequently, eculizumab is considered one of the world's most expensive drugs. Second, the burden for patients is considerable since eculizumab has to be administered intravenously every 2 weeks, potentially for a lifetime. Third, there are large interindividual variations in pharmacokinetics (PK) [9, 10], and, lastly, treatment is not without risks. The most prominent risk is the susceptibility to infection with *Neisseria meningitidis* (meningococcus) [11]. Furthermore, evidence is accumulating regarding the potential (long-term) adverse effects of eculizumab, such as hepatotoxicity [12, 13].

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Table 1 Reported use of eculizumab in light of pharmacokinetic and pharmacodynamic data

Disease	Pharmacokinetic data available ^a	Pharmacodynamic data available ^b	References
Atypical hemolytic uremic syndrome	Yes	Yes	[6, 9, 10, 52, 53, 56, 60, 61, 75, 82, 86–92]
Paroxysmal nocturnal hemoglobinuria	Yes	Yes	[1, 2, 16, 32, 42, 57, 59, 68, 73, 74, 93–98]
Refractory generalized myasthenia gravis	Yes	Yes	[5, 36, 99]
Shiga toxin producing <i>Escherichia coli</i> hemolytic uremic syndrome	No	No	[29, 100]
Multifocal motor neuropathy	Yes	Yes	[62]
Antibody-mediated kidney rejection	No	No	[48, 101]
C3 glomerulopathy (including dense deposit disease)	Yes	No	[22, 26]
Age-related macular degeneration	Yes	No	[28, 102]
AQP4 IgG-positive neuromyelitis optica	Yes		[45]
Systemic lupus erythematosus	Yes	Yes	[43]
HSCT-TMA	Yes	Yes	[18, 25, 30]
Guillain-Barré	No	No	[103]
Psoriasis	Yes	No	[3]
Rheumatoid arthritis	Yes	Yes	[3, 44, 73]
Dermatomyositis	Yes	No	[46]
Idiopathic membranous glomerulopathy	Yes	Yes	[3, 73]
Demyelinating neuropathy with CD59 p.Cys89Tyr mutation	No	No	[104]

HSCT-TMA hematopoietic stem cell transplantation-associated thrombotic microangiopathy, *Ig* immunoglobulin

^aData on serum eculizumab (trough) levels were considered sufficient for pharmacokinetic data

^bData regarding serum eculizumab levels in relation to complement blockade

Taking these factors into consideration, the infinitesimal data regarding dose adaptations guided by either measuring drug concentration or efficacy markers (complement system) is striking. In this review, we provide insight into the PK and pharmacodynamics (PD) of eculizumab, for both reported on- and off-label use. Furthermore, PK targets within different diseases are discussed to optimize dosing. To conclude, the possibility, and above all necessity, of dose individualization will be discussed, together with the tools to achieve tailored patient care.

1.1 The Complement System

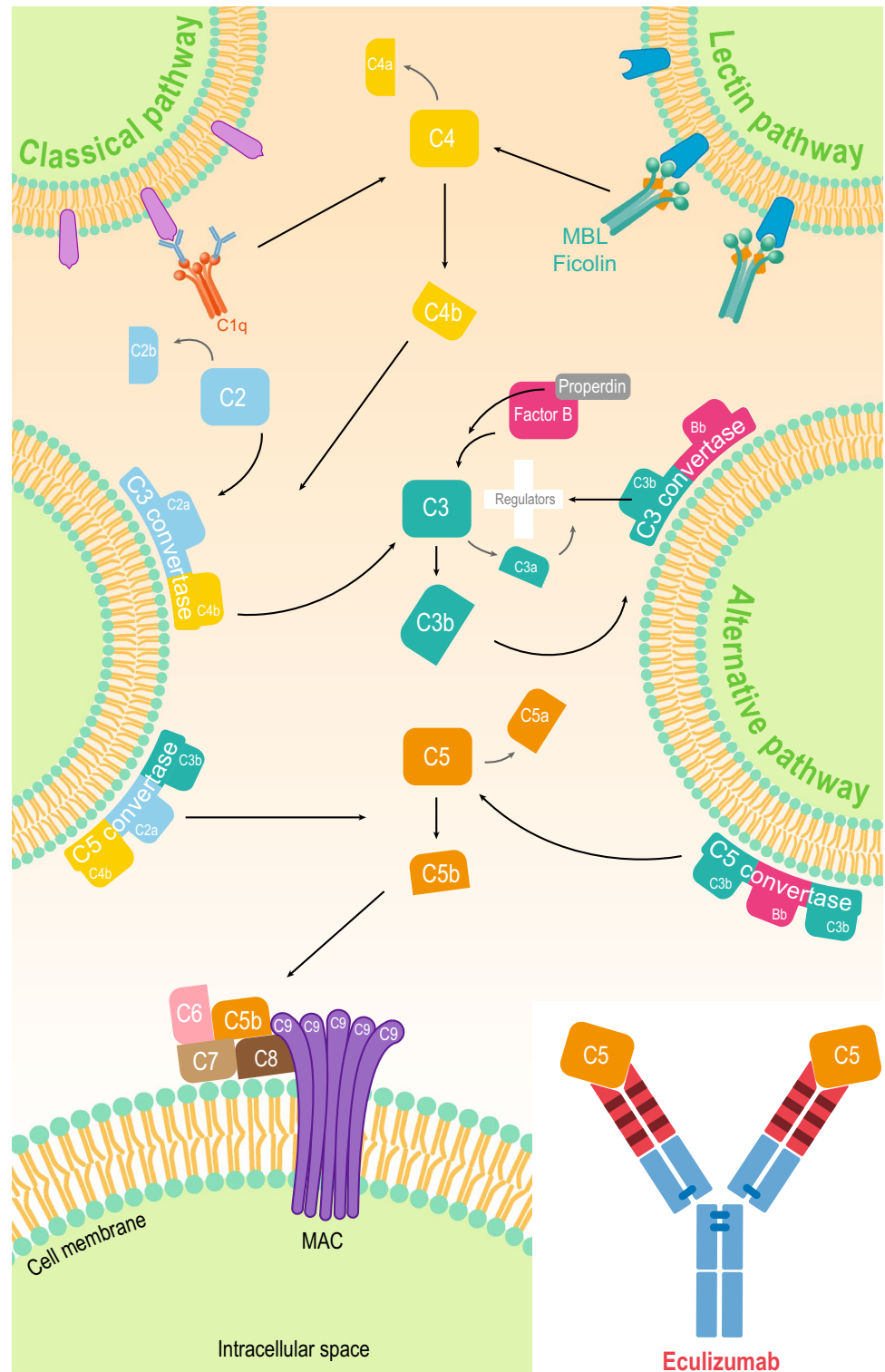
The complement system is an important part of innate immunity and consists of three different pathways, all converging at C3, the central complement component (Fig. 1). The classical pathway (CP) and lectin pathway (LP) are, respectively, triggered by antibodies (such as the case in gMG) and mannose-containing sugars on pathogens. The alternative pathway (AP) is unique since spontaneous auto-activation is always present and can be further triggered by bacterial components such as lipopolysaccharide and bacterial toxins [14]. Activation of each pathway leads to the formation of the C3 convertase (C3bBb) which can cleave

C3, leading to chemotaxis and opsonization with C3a and C3b, respectively. The generation of large amounts of C3b results in the formation of C5 convertase (C3bBbC3b). In turn, C5 convertase can cleave C5, thereby producing the second anaphylatoxin C5a, and C5b, which can bind complement proteins C6, C7, C8 and C9 to form the end product of the complement system, the membrane attack complex or C5b-C9 (C5b-C9), which causes cell lysis (Fig. 1). Normally, the complement system is tightly controlled by regulatory proteins present in both the fluid phase and on the cell surface [14, 15].

1.2 Pathogenesis of Complement-Mediated Diseases

Together with our growing knowledge of the complement system and its role in different diseases, evidence has emerged for complement blockade with drugs. Eculizumab was approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) as standard treatment for PNH, aHUS and gMG in 2007, 2011, and 2017, respectively [1, 6, 16, 17]. Eculizumab administration is reported in two disease situations: primarily in diseases resulting from complement dysregulation (e.g. PNH and

Fig. 1 The complement system, which consists of three pathways that all converge at C3. The classical pathway is depicted in the left upper quadrant, the lectin pathway is depicted in right upper quadrant, and the alternative pathway is depicted in the middle on the right. After activation, C3 convertases (C2aC4a or C3bBb) are formed, and subsequently C5 convertases (C2aC4bC3b or C3bBbC3b), resulting in the formation of the lytic pore and end product of the complement system (C5b-C9). To prevent overactivation, the complement system is tightly controlled by various complement regulators such as factor H and factor I. Eculizumab is a humanized (chimeric) monoclonal antibody and is able to bind one or two C5 molecules, thereby preventing the cleavage of C5 into C5a and C5b, and hence blocking formation of C5b-C9. *Fb* factor b, *MAC* membrane attack complex, *MBL* mannose binding lectin



aHUS) and subsequently in diseases with extensive complement activation with inflammation (e.g. gMG) [18–30]. For the purpose of this review, the most prominent diseases with reported eculizumab therapy are described, in light of sufficient PK and PD data being available.

1.2.1 Paroxysmal Nocturnal Hemoglobinuria

PNH is a rare form of acquired hemolytic anemia associated with high mortality and morbidity. It has an estimated incidence of one to two cases per million and usually affects

adult patients [31, 32]. PNH is caused by a non-malignant clonal expansion of hematopoietic stem cells containing a somatic mutation in a gene located on the X-chromosome called phosphatidylinositol glycan complementation class A [2]. As a result, affected stem cells are deficient of glycosyl phosphatidylinositol anchored proteins. In patients with PNH, clonal expansion results in the production of cells, such as erythrocytes, granulocytes and platelets, that lack the expression of glycosyl phosphatidylinositol anchored complement regulatory proteins CD55 and CD59. Due to the absence of complement regulators CD55 and CD59, erythrocytes are susceptible for complement activation on the cell surface, in particular causing hemolysis and thrombosis [15]. Before the era of eculizumab, thrombosis accounted for up to 65% of deaths, with a thrombosis incidence of 29–44% [31].

1.2.2 Atypical Hemolytic Uremic Syndrome

Atypical HUS is a rare and severe form of thrombotic microangiopathy (TMA) resulting in mechanical hemolytic anemia, thrombocytopenia, and acute kidney injury [33]. Atypical HUS results from an uncontrolled overactivation of AP due to pathogenic mutations of, or acquired autoantibodies directed against, complement regulatory proteins. This complement dysregulation causes endothelial activation and injury, resulting in platelet aggregation, formation of thrombi, and mechanical hemolysis. Atypical HUS has an estimated incidence of 0.23–0.42 cases per million and affects all ages, with a slightly higher incidence in childhood when compared with adults [34]. Although TMA affects predominantly the renal vasculature, extrarenal involvement is reported [33, 35]. Before the implementation of eculizumab, mortality was as high as 25% in the acute phase of the disease and over 50% of patients reached end-state renal disease after their first presentation.

1.2.3 Refractory Generalized Myasthenia Gravis

Generalized MG is a rare and acquired form of neuromuscular autoimmune disorder. It occurs in the presence of antibodies, and up to 80% is directed against the acetylcholine receptor at the postsynaptic membrane of the neuromuscular junction. Antibodies (immunoglobulin [Ig] G1 and IgG3 isotypes) are known to activate CP, ultimately leading to C5b-C9 deposition on the postsynaptic membrane, and consequently disruption of the acetylcholine receptors. Due to chemotaxis and cell lysis associated with complement activation, the postsynaptic membrane becomes less sensitive to the released acetylcholine, hence nerve impulses will be inhibited [36–39]. Generalized MG has an estimated incidence of up to 10 per million, and patients experience

progressive muscle weakness and fatigue. Due to respiratory failure, patients are frequently admitted to the intensive care unit, and, in the case of delayed intervention, this can eventually lead to death [36, 37].

1.2.4 Hematopoietic Stem Cell Transplantation-Associated Thrombotic Microangiopathy

Secondary TMA is frequently seen in patients after hematopoietic stem cell transplantation (HSCT) [18]. Mimicking aHUS, the complement system plays a crucial role in developing severe HSCT-TMA [18, 25, 40]. Particularly in patients presenting with severe HSCT-TMA, the mortality rate and severity of chronic sequelae are high. Severe TMA affects 20–30% of HSCT recipients and is characterized by proteinuria and elevated levels of sC5b-C9, in addition to TMA.

2 Method

A literature search of both the PubMed and Embase electronic databases was performed in May 2017. The specific strings used for both search engines are rendered below. The main search terms were ‘eculizumab’, ‘pharmacokinetics’, and ‘pharmacodynamics’. In total, 73 and 766 articles were found in PubMed and Embase, respectively, and titles were screened by KW, followed by screening of the abstract and full text. We excluded languages other than English and Dutch (35), duplicates (65), case reports that included less than four cases (81), articles in which no full-text was available (19), and articles that did not include PK or PD data (526). Furthermore, we choose to focus on a limited number of diseases (namely PNH, aHUS, HSCT-TMA, and gMG). Miscellaneous articles were added to supply background information and additional PK and PD information as supplied to the EMA and FDA.

2.1 PubMed

((“Eculizumab” [Supplementary Concept] OR eculizumab[tiab] OR soliris[tiab]) AND (“pharmacology” [Subheading] OR “Pharmacology, Clinical”[Mesh] OR “Pharmacokinetics”[Mesh] OR “Drug Interactions”[Mesh] OR “Dose-Response Relationship, Drug”[Mesh] OR Pharmaco*[tiab] OR exposure*[tiab] OR drug monitoring[tiab] OR drug concentration*[tiab] OR target concentration*[tiab] OR clinical pharmacolog*[tiab] OR drug interact*[tiab] OR adverse effect*[tiab] OR adverse event*[tiab] OR adverse drug event*[tiab] OR contraindication*[tiab] OR contra-indication*[tiab] OR dose-response[tiab]))

2.2 Embase

[Adverse Drug Reaction, Drug Administration, Drug Concentration, Drug Dose, Drug Therapy, Drug Toxicity, Intravenous Drug Administration, Pharmaceuticals, Pharmacokinetics, Pharmacology]

(exp eculizumab/ae, ad, cr, do, dt, to, iv, pr, pk, pd) OR (Eculizumab OR soliris).ti,ab,kw.

AND exp drug exposure/ or exp drug safety/ or exp pharmacodynamics/ or exp pharmacokinetics/ or exp clinical pharmacology/ or pharmacokinetic*.ti,ab,kw. or pharmacodynamic*.ti,ab,kw. or drug interact*.ti,ab,kw. or adverse effect*.ti,ab,kw. or adverse event*.ti,ab,kw. or adverse drug event*.ti,ab,kw. or contraindication*.ti,ab,kw. or contraindication*.ti,ab,kw. or dose-response.ti,ab,kw.

3 Pharmacokinetic (PK) Properties of Eculizumab

Eculizumab (Soliris[®], Alexion Pharmaceuticals, Inc., New Haven, CT, USA) is a humanized chimeric monoclonal antibody consisting of a human framework build of IgG2 and IgG4 composed of variable regions of murine origin (Fig. 1). The eculizumab dose depends on the indication and weight of the patient (dose adjustment for patients with a body weight < 40 kg). The PK of eculizumab in healthy subjects have not been studied [41]. In 1999, phase I studies were performed in rheumatoid arthritis (RA; C97-001-01) and systemic lupus erythematosus (SLE; C97-002-01) patients, followed by phase II multiple-dose studies in 2002 conducted in patients with RA (C01-004), idiopathic membranous glomerulopathy (IMG, C99-004), and PNH (C02-001). Pilot studies have also been performed in patients with dermatomyositis (C99-007) and psoriasis (C99-007) [42–48].

3.1 Absorption, Distribution, Metabolism, and Excretion

The characteristics of eculizumab are similar to other monoclonal antibodies. Eculizumab is administered as an intravenous infusion in 25–45 min, with a maximum of 2 h and 4 h in patients > 12 and < 12 years of age, respectively (see Table 2 for different dosage regimens for each disease) [41]. After intravenous administration, eculizumab is primarily distributed in blood plasma. Limited distribution in cerebrospinal fluid has been described, with concentrations 5000-fold lower than in plasma [45]. Distribution to other tissues has not been described in human studies. In vivo animal studies and in vitro studies with normal human tissues

showed intracellular distribution to a wide variety of cells, consistent with expected C5 localization.

As described for other monoclonal antibodies, eculizumab is internalized by either pinocytosis or binding to the Fcγ receptor, and is subsequently degraded by lysosomes to peptides and amino acids. Recycling of eculizumab can occur via binding to the neonatal Fc receptor (FcRn). However, the eculizumab–C5 complex does not dissociate efficiently in the endosome. Hence, eculizumab catabolism is mainly driven by target-mediated drug disposition [49]. Eculizumab contains no known active metabolites [41, 50, 51]. Due to its molecular size, eculizumab is not excreted in urine, except in patients with heavy proteinuria, where eculizumab concentrations as high as 56 μg/ml have been detected [52, 53].

3.2 Eculizumab Population PK Analysis

The eculizumab concentration in serum depends on various factors. The dose is based on weight and the underlying disease, with the exception of patients with a body weight < 40 kg; this group receives a weight-based regimen. To identify the optimal dose of eculizumab necessary to block complement, six single-dose studies were performed in patients with RA (C97-001-01) and SLE (C97-002-01) [3]. Patients were infused with a single dose, ranging from 0.1 to 8 mg/kg of eculizumab in 30 min (Tables 3, 4). As reported in the scientific discussion of the EMA, these single-dose studies in RA patients yielded a mean clearance (CL) of 0.26 ml/kg/h, with a central volume of distribution (Vd1) of 15 ml/kg and peripheral volume of distribution (Vd2) of 20 ml/kg [42]. The estimated Vd at steady state was calculated at 35 ml/kg, and, with this Vd, the estimated half-life was 93 h (3.9 days). The area under the curve (AUC) was calculated at 24,467.6 μg·h/ml. A twofold increase in the eculizumab dose from 4 to 8 mg/kg in RA and SLE yielded an increase of 60% and 15% in mean maximum concentration (C_{max}), respectively (Table 3). Furthermore, the AUC increased by 70% and 103% in RA and SLE, respectively (Table 3). Both distribution and half-life were dose-dependent (Table 3) [3, 42]. One highly interesting observation was the presence of a second peak after 2 days postdose, which was most likely related to drug recycling from the endosome back into the bloodstream, as described for other monoclonal antibodies [54]. This peak is most often seen in single-dose, phase I or II studies due to timing of blood sampling, which is more frequent. The concentration of this second peak is minimal compared with the first peak and does not impact the overall drug exposure or complement inhibition; thus, it is presumed not to be therapeutically significant (Alexion, personal correspondence) [54].

Table 2 Dosage scheme in different patient populations

Patient group	Induction	Maintenance
PNH	600 mg every week for 4 weeks	900 mg in the fifth week, every 14 days thereafter
aHUS-gMG	900 mg every week for 4 weeks	1200 mg in the fifth week, every 14 days thereafter
Pediatric population PNH and aHUS < 40 kg		
30 to < 40 kg	600 mg every week for 2 weeks	900 mg in the third week, every 14 days thereafter
20 to < 30 kg	600 mg every week for 2 weeks	600 mg in the third week, every 14 days thereafter
10 to < 20 kg	300 mg once	300 mg in the second week, every 14 days thereafter
5 to < 10 kg	300 mg once	300 mg in the second week, every 21 days
HSCT-TMA	900 mg, second dose when: ^a	1200 mg every 2 weeks, when steady CH50 suppression is achieved and TMA parameters, together with sC5b-C9 levels, normalize
Pediatric population < 40 kg		
30 to < 40 kg	600 mg second dose when ^a	900 mg every 2 weeks, when steady CH50 suppression is achieved and TMA parameters, together with sC5b-C9 levels, normalize
20 to < 30 kg	600 mg second dose when ^a	600 mg every 2 weeks, when steady CH50 suppression is achieved and TMA parameters, together with sC5b-C9 levels, normalize
10 to < 20 kg	600 mg second dose when ^a	300 mg every 2 weeks, when steady CH50 suppression is achieved and TMA parameters, together with sC5b-C9 levels, normalize
5 to < 10 kg	300 mg second dose when ^a	300 mg every 2 weeks, when steady CH50 suppression is achieved and TMA parameters, together with sC5b-C9 levels, normalize

aHUS atypical hemolytic uremic syndrome, CH50 classical pathway inhibition, gMG generalized myasthenia gravis, HSCT hematopoietic stem cell transplantation, PNH paroxysmal nocturnal hemoglobinuria, sC5b-C9 soluble C5b-C9, TMA thrombotic microangiopathy

^aWithin 72 h when sC5b-C9 is > 244 ng/mL, when CH50 was no longer suppressed, or after 7 days. In case of the remaining complement activity (CH50 > 10% and elevated sC5b-C9, the dose should be increased by 300 mg/dose to a maximum of 1200 mg/dose [18])

Table 3 Non-compartmental analysis

Population	No. of participants	Eculizumab dosage (mg/kg)	Clearance (ml/h) ± SD	Central volume of distribution (ml) ± SD	AUC _∞ (μg·h/ml) ± SD	C _{max} (μg/ml) ± SD	C _{trough} (μg/ml) ± SD	Half-life (h) ± SD	References
RA (C97-001)	6	4	16.2 ± 7.2	7500 ± 4700	22,200 ± 13,700	111 ± 53	Unknown	281 ± 298	[3]
RA (C97-001)	6	8	20.3 ± 7.2	5000 ± 3600	37,800 ± 5900	182 ± 19	Unknown	197 ± 198	[3]
SLE (C97-002)	3	4	19.3 ± 5.2	4200 ± 1500	15,600 ± 5000	139 ± 25	Unknown	162 ± 88	[3]
SLE (C97-002)	3	8	19.1 ± 8.1	3900 ± 1800	31,600 ± 9100	160 ± 10	Unknown	141 ± 6	[3]
aHUS patients with PT (C08-003, C09-001r)	48	See Table 2	3660	Unknown	Unknown	Unknown	Unknown	1.26	[56, 61]
Pediatric aHUS patients (C10-003)	22	See Table 2	10.4	5230	Median 141,741.4 (range 43,652.9– 261,814.4)	515.4 (range 264.7– 1094.4)	256.7 (range 50.2– 531.1)	290	[60]

aHUS atypical hemolytic uremic syndrome, AUC_∞ area under the curve from time zero to infinity, C_{max} maximum concentration, C_{trough} trough concentration, PT plasmatherapy, RA rheumatoid arthritis, SD standard deviation, SLE systemic lupus erythematosus

Table 4 Population pharmacokinetic analyses

Population	No. of participants	Clearance (ml/kg/h \pm SD)	Central volume of distribution (ml/kg \pm SD)	Peripheral volume of distribution (ml/kg \pm SD)	Intercompartmental clearance (ml/kg/h)	Elimination constant (1/h)	Half-life (h) \pm SD	Effect of weight on Vd	References
RA (C97-001)	10	0.262	15.04	20	Unknown	Unknown	92.9	NA	[42]
RA (C97-001)	121	0.3 \pm 0.12	12.7 \pm 8.54	42.3 \pm 9.7	0.54 \pm 0.16	Unknown	Unknown	NA	[73]
SLE (C97-002)	6	0.3 \pm 0.11	18.7 \pm 4.8	20.6 \pm 10.84	0.59 \pm 0.56	Unknown	Unknown	NA	[73]
RA (C01-004)	111	0.230	12.5	44.4	Unknown	Unknown	131.33	NA	[42]
IMG (C99-004)	71	0.41 \pm 0.14	64.9 \pm 31.5	149.5 \pm 44.92	0.21 \pm 0.17	Unknown	Unknown	NA	[73]
PNH (C02-001)	11	0.25 \pm 0.069	32.5 \pm 16.5	26.5 \pm 7.37	0.21 \pm 0.06	Unknown	Unknown	NA	[73]
PNH (C04-001)	40	0.311 \pm 0.13	110.3 \pm 17.9	NA	NA	0.0028 \pm 0.0008	271.7 \pm 81.6	NA	[73]
gMG (ECU-MG-301, C08-001)	75	7.37 ml/kg [95% CI 6.62–8.2]	2210 ml [95% CI 1940– 2530]	2400 ml [95% CI 2040–2820]	182 ml/h [95% CI 73.3–454]	Unknown	Unknown	0.634 [95% CI 0.494– 0.774]	[5]
aHUS (C08-002, C08-003, C09-001r)	57	0.208	87.7	NA	NA	Unknown	291	NA	[56, 61]
HSCT-TMA	18	1.4 (RSE of 9%)	81.7 (RSE of 21%)	NA	NA	Unknown	Unknown	NA	[18]

aHUS atypical hemolytic uremic syndrome, *CI* confidence interval, *gMG* generalized myasthenia gravis, *HSCT-TMA* hematopoietic stem cell transplantation-associated thrombotic microangiopathy, *IMG* idiopathic membranous glomerulopathy, *NA* not applicable, *PNH* paroxysmal nocturnal hemoglobinuria, *RA* rheumatoid arthritis, *RSE* relative standard error, *SD* standard deviation, *SLE* systemic lupus erythematosus, *Vd* volume of distribution

Multiple-dose studies were conducted in three patient groups with RA (C01-004), IMG (C99-004), and PNH (C02-001). With the use of a two-compartment model, PK parameters were calculated (see Table 4). At therapeutic doses, eculizumab shows linear PK, indicating saturation of the drug target [42].

The population PK of eculizumab in PNH patients have previously been described using a one-compartment model (Table 4). CL was estimated to be 0.3 ml/kg/h, with a Vd of 110.3 ml/kg, which was slightly larger than the estimated serum volume of patients [3]. The elimination rate (*K*) was 0.0028 1/h, which resulted in a half-life of approximately 271.7 h (11.3 days). Of note, in the study by de Latour et al., trough concentration (C_{trough}) varied from 18 to 643 $\mu\text{g/ml}$ and half-life was highly variable, ranging from 4 to 21 days [55]. In PNH, eculizumab C_{trough} measured at week 26 was $97 \pm 60 \mu\text{g/ml}$. C_{trough} levels remained stable during the maintenance phase (see Table 2 for the dosing regimen) [3,

56]. During the follow-up of patients in both pivotal trials (extension study, E05-001), C_{trough} concentrations $< 35 \mu\text{g/ml}$ were repeatedly observed in 10% of patients; this correlated with rapid eculizumab CL $> 0.4 \text{ ml/kg/h}$ or a shorter half-life $< 130 \text{ h}$. In half of the patients, breakthrough hemolysis was successfully treated by decreasing the eculizumab dosing interval. Overall, 10% of patients needed frequent changes in dosing interval to sustain remission [57].

In the group of aHUS patients, PK were best described using a one-compartment model. In total, 57 patients from C08-002A/B, C08-003 A/B, and C09-001r were included in the analysis (see Tables 3 and 4). CL was estimated at 0.2 ml/kg/h and Vd was 87.7 ml/kg. C_{trough} concentrations measured at week 26 in aHUS were $242 \pm 101 \mu\text{g/ml}$, with an estimated half-life of 291 h (12.1 days) [56]. PK data of both prospective trials (C08-002 A/B and C08-003 A/B) showed C_{trough} levels of 93 and 113 $\mu\text{g/ml}$, respectively, in adults, and 104 and 109 $\mu\text{g/ml}$, respectively, in adolescent

patients. The AUC during the maintenance phase in both trials was 77,693 $\mu\text{g}\cdot\text{h}/\text{ml}$ and 104,228 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively, in adults, and 104,228 $\mu\text{g}\cdot\text{h}/\text{ml}$ and 99,956 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively, in adolescents. The observed C_{max} was up to 431 $\mu\text{g}/\text{ml}$ [56].

The PK properties of eculizumab in gMG were best described using a two-compartment model (see Table 4) [5, 38, 58]. Data from two studies were combined to best describe the PK. Fourteen participants from a double-blind, placebo-controlled, randomized, crossover trial (C08-001) and 126 participants from a double-blind, placebo-controlled, randomized trial (ECU-MG-301) were included in the analysis. CL was estimated at 0.09 ml/kg/h, with a Vd1 of 27.6 ml/kg and Vd2 of 30 ml/kg (median weight of 80 kg in the eculizumab arm). Eculizumab C_{trough} concentrations were approximately twofold different at steady state when comparing both studies. Following a maintenance dose of 1200 mg, C_{max} and C_{trough} levels reported at week 26 were $738 \pm 288 \mu\text{g}/\text{ml}$ and $341 \pm 172 \mu\text{g}/\text{ml}$. Interindividual variability was high, and CL and Vd were up to 42% and 24%, respectively [5, 58].

Finally, another study assessed the PK properties of eculizumab in patients with HSCT-TMA. Eculizumab CL ranged from 0.23 to 3.39 mL/kg/h during the induction phase. Important to note is the high number of erythrocyte and platelet transfusions due to severe and persistent gastrointestinal bleeding, which explains the high CL rate. At the fifth week, CL decreased to a mean CL (\pm standard deviation [SD]) of 0.35 ml/kg/h (± 0.25). PK modeling with a one-compartment model of eculizumab therapy in HSCT recipients showed a high variability of eculizumab CL of 1.4 ml/kg/h (relative standard error 9%), especially within the first weeks of treatment [18].

3.3 Factors Influencing Eculizumab Concentrations

Several covariates have been identified to impact the PK of eculizumab, including age, weight, C5 concentrations, C5b-C9 concentrations, human anti-human antibodies (HAHAs), plasma exchange therapy, and pregnancy. The impact of these covariates will be discussed in the next paragraphs.

3.3.1 Effect of Age and Weight

The most important covariate is body weight of the patient, especially in the pediatric population [9]. Consequently, in patients with a body weight < 40 kg, the eculizumab dose scheme is adjusted. Eculizumab PK in children have been investigated in two open-label studies, in both PNH ($n = 7$) and aHUS ($n = 22$) patients [59, 60].

In the open-label, phase I/II study (M07-005) conducted in seven PNH patients ranging in age from 11 to 17 years, patients received eculizumab according to the standard protocol

(600 mg weekly for 4 weeks, followed by 900 mg at week 5 and every 14 days thereafter). Eculizumab concentrations reached a plateau after 4 weeks. After 12 weeks, the median C_{trough} concentrations were 192.5 $\mu\text{g}/\text{ml}$ (range 124.2–321.1), with a median C_{max} of 425.4 $\mu\text{g}/\text{ml}$ (220.5–556.1) [59]. No data regarding CL and Vd were described.

Based on population PK analysis of the three pivotal trials of aHUS (C08-002, C08-003, and C09-001r), CL (\pm SD) per weight category (> 40, 30–40, 20–30, 10–20, and 5–10 kg) was estimated at 15.1 (± 6.5), 7.6, 6 (± 1.46), 5.49 (± 0.24), and 3.6 (± 1.3) ml/h, respectively, resulting from an allometric relationship between weight and CL [56]. Furthermore, in the prospective, open-label, non-randomized, single-arm C10-003 trial, 22 pediatric aHUS patients > 1 month of age and a body weight of 4.9 kg were included [60]. Median weight was 20 kg (range 7–95 kg). Patients received different doses of eculizumab, with an interval of 14–21 days based on weight, as described in the summary of product characteristics [61]. CL and Vd were 0.54 ml/kg/h and 261.5 ml/kg (based on a median weight of 20 kg), respectively [60]. Overall, patients had a C_{max} of 515.4 $\mu\text{g}/\text{ml}$ (range 264.7–1094.4) and C_{trough} of 256.7 $\mu\text{g}/\text{ml}$ (range 50.2–531.1), which is higher than in the adult population. The elimination half-life was 290 h (12 days). Overall, patients had a median AUC of 141,741.4 $\mu\text{g}\cdot\text{h}/\text{ml}$ (range 43,652.9–261,814.4) at steady state. The power function of body weight on CL and Vd was estimated at 0.796 (95% confidence interval [CI] 0.6–0.99) and 0.715 (95% CI 0.59–0.84), respectively. Eculizumab appeared safe and effective in pediatric patients [41, 60].

3.3.2 C5 Concentration

One eculizumab molecule can bind two C5 molecules. Since eculizumab–C5 complexes are not recycled via FcRn, C5 levels influence the target-mediated drug disposition of eculizumab. C5 levels are approximately 80–110 $\mu\text{g}/\text{ml}$ in healthy controls, but are highly variable per individual and per time point depending on the underlying disease and the amount of complement activation [10].

3.3.3 Soluble C5b-9 Levels

Three articles were recently published suggesting that soluble C5b-9 (sC5b-C9) levels may impact eculizumab exposure [10, 18, 52]. Since eculizumab is capable of not only binding C5 but also sC5b-C9 with lower affinity, it is physiologically plausible that increased levels of sC5b-C9 at the initiation of therapy correlate with lower eculizumab concentrations. Jodele et al. even showed that pretreatment-measured sC5b-C9 levels correlated with eculizumab CL [18].

3.3.4 Intravenous Administration of Immunoglobulins

Monoclonal antibodies can be cleared via non-specific endocytosis and uptake via Fc γ receptors on phagocytes; however, they are protected intracellularly from degradation by the FcRn. In case of saturation of this FcRn, due to, for example, a high load of immunoglobulins, increased elimination of monoclonal antibodies can occur [50]. A study performed in patients with multifocal motor neuropathy, who were treated with eculizumab according to PNH protocol, and concomitant intravenous immunoglobulins (IVIgs), showed a significantly lower eculizumab C_{trough} . Eculizumab concentrations were measured in patients who received IVIg therapy, and a median of 79 $\mu\text{g/ml}$ (interquartile range [IQR] 55–108) was reported, versus 120 $\mu\text{g/ml}$ (IQR 96–147) in patients who did not receive IVIg [62]. No statistical significance was observed in hemolytic complement activity, although more patients with IVIg had detectable total complement activity > 20% [62].

3.3.5 Human Anti-human Antibodies

As with any humanized antibody therapy, the risk of developing (neutralizing) HAHA is present. Analysis of a cohort of 75 PNH patients with a median of 7.5 years of eculizumab therapy revealed no HAHA [63]. In the TRIUMPH trial, one patient developed HAHA, however this did not seem to affect eculizumab therapy [1]. One aHUS patient aged 30 months was reported as developing HAHA; this patient had inadequate C_{trough} (17.1 $\mu\text{g/ml}$), ongoing hemolytic activity, and non-responsive TMA after the start of treatment [60].

3.3.6 Plasma Infusion and Exchange

As expected, plasma exchange and plasma infusion have a clear influence on the CL of eculizumab, and subsequently led to a marked reduction in half-life (see Table 3). CL was measured in aHUS patients with plasma exchange and increased from 14.6 to 3660 ml/h, with an estimated half-life of 1.26 h. Therefore, it is recommended to supplement an extra dose of eculizumab (600 mg, unless the patient only received 300 mg in the maintenance phase, and then only 300 mg of supplementation) within 60 min after plasma exchange. In case of infusion of fresh frozen plasma, it is recommended to administer 300 mg, in addition to the normal dose, 60 min prior to infusion [41, 58].

3.3.7 Effect of Pregnancy

No formal PK studies have been performed for pregnant women receiving eculizumab. Different articles and case reports describe the use of eculizumab in pregnant women

with either PNH or aHUS [64–70]. Kelly et al. reported therapeutic concentrations of eculizumab measured in two of three PNH patients, without detectable eculizumab in cord blood and breast milk [68]. Furthermore, Servais et al. described five pregnancies in three aHUS patients receiving eculizumab, and, as similarly reported by Kelly et al., no eculizumab was detected in cord and neonatal blood; however, the eculizumab dose had to be increased in two patients, as high as 1800 mg every 2 weeks, to maintain complement blockage. Both patients showed signs of partial blockage in the first trimester [69]. In contrast to the previously discussed studies in a cohort of 61 pregnant PNH patients, in 35% of the cord blood samples eculizumab concentrations were detectable, ranging from 11.8 to 21.2 $\mu\text{g/ml}$, which is in contrast to the breast milk samples where eculizumab was not detectable [70]. Moreover, pregnancy was associated with lower, and even inadequate, C_{trough} levels of eculizumab. Of the 61 patients evaluated, half needed an increased dose of eculizumab [70].

4 Pharmacodynamic (PD) Properties of Eculizumab

Formal dose and concentration response studies were not performed in any of the patient groups reported below. Data from various clinical trials were used to assess the efficacy and exposure–response of eculizumab; however, only the data published regarding PD in relation to PK will be described in this review.

4.1 Monitoring of Eculizumab Therapy

In all trials conducted by the pharmaceutical company, hemolytic activity was used to determine the PD properties of eculizumab [6, 60]. Hemolytic activity reflects total complement activity (reported as CH50) by testing the capacity of patient serum to lyse sheep or chicken erythrocytes coated with antibodies. In case of a functional complement system, the CP will be activated, subsequently leading to C5b-C9 deposition on the erythrocytes and thus causing hemolysis. CH50 levels correlated with eculizumab serum trough levels, and a completely blocked complement (no hemolytic activity measured) was the aim of treatment.

It is important to realize that besides the classical hemolytic assay based on lysis of erythrocytes, various other assays have been introduced to measure CH50. Furthermore, C5 function and AP activity (AP50) are also reported as a marker of eculizumab effectiveness [71]. In case of eculizumab levels > 100 $\mu\text{g/ml}$, undetectable CH50, AP50, and normal C5 levels with inhibited C5 function have been reported [71]. There are different (commercial) assays available to measure these markers, of which the so called

'Wieslab' ELISA is quite commonly used. However, more studies are needed to explore the relation between AP50 and eculizumab trough levels since AP50 levels are not totally suppressed despite high eculizumab levels [71, 72].

4.2 Exposure–Effect Relationship of Eculizumab

The exposure–effect relationship in the phase I and II trials in RA, SLE, and IMG patients was mainly evaluated using the serum hemolytic activity to assess complement inhibition [3]. The results of the single-dose studies in RA (C97-001) and SLE (C97-002) showed a concentration-dependent inhibition of hemolytic activity, with an inverse relationship between eculizumab concentration and C5 complement blockade. Hemolytic activity was completely blocked within 15 min in almost all patients who received a 2.0 mg/kg dose, but hemolytic activity reappeared within 2 days. By increasing the dose to 4 or 8 mg/kg, complement activity was completely suppressed for 7–14 and 11–21 days, respectively. Complete blockade of complement hemolytic activity was measured at eculizumab concentrations as low as 29–55 µg/ml and 11–35 µg/ml in RA and SLE patients, respectively [3].

The maximum PD effect was modeled using a maximum effect (E_{\max}) model using the above-described data from RA patients pooled with data of IMG and PNH patients, with a half maximal effective concentration (EC_{50}) of 43 µg/ml (95% CI 39.04–47.78) [3]. Since eculizumab concentrations are reported in both the bound to C5 and unbound proportion of eculizumab, this could indicate an overestimation of the required eculizumab concentration for complement blockade [73]. The EMA scientific report using pooled data from all single- and multiple-dose studies (performed in various patient populations) suggested that an eculizumab serum concentration of 35 µg/ml is sufficient to completely block complement activation. Hence, the dosing schedule of 600 mg in the initiation phase, followed by 900 mg every 2 weeks, was selected as the most optimal dosing regimen to suppress complement inhibition in almost all PNH patients (Table 2) [3, 42].

Nonetheless, based on a meta-analysis of data from 177 PNH patients, a higher target exposure was recommended for patients with aHUS. In this cohort of PNH patients, some patients (up to 10%) had remaining complement activity [16, 57]. It was expected that this residual activity could result in clinical manifestations in the aHUS patient group. The main expected clinical manifestations reported were the potential rapid loss of kidney function in case of insufficient blockade, with ongoing active TMA [61]. In the FDA approval package, an analysis is shown that describes the necessity of a minimal eculizumab concentration of 50 µg/ml to achieve a > 90% decrease in free C5 [56]. Hence, in aHUS patients,

higher eculizumab concentrations of 50–100 µg/ml for complete complement blockade are recommended (Table 2).

4.2.1 Paroxysmal Nocturnal Hemoglobinuria

Different trials, i.e. C02-001 ($n = 11$), TRIUMPH ($n = 43$) and SHEPHERD ($n = 97$), as well as the extension trial comprising all previously reported patients (E05-001), reported efficacy of eculizumab in PNH [1, 2, 74]. To assess PD properties, serum hemolytic activity was evaluated. Unfortunately, both the TRIUMPH and SHEPHERD trials mentioned the use of the serum hemolytic assay, however no values were reported [1, 16]. Eculizumab concentrations in relation to hemolytic activity were only described in the extension trial. In total, 43 patients from the TRIUMPH trial and 97 patients from the SHEPHERD trial were included. Overall, 36% of patients had eculizumab concentrations < 35 µg/ml after the first infusion of eculizumab [57], of whom 36% and 74% exhibited hemolytic activity (> 20%). During the follow-up period, C_{trough} concentrations < 35 µg/ml were repeatedly observed in 14 (10%) patients. In half of these patients, complement activity was blocked by decreasing the interval between administrations. In total, 21 patients from the entire population experienced a median of 22 decreases in dosing interval [57].

Reiss et al. described the results of a phase I/II study in seven pediatric PNH patients, all > 11 years of age. Eculizumab concentrations > 124 µg/ml correlated with complete complement blockade. The C_{max} and C_{trough} concentration, together with the AUC of eculizumab, were associated with a change in lactate dehydrogenase (LDH) [59].

de Latour et al. assessed the efficacy of eculizumab in 22 PNH patients [55]. The association between CH50 and LDH was assessed using a linear mixed model with intercept and slope for therapy duration. The association between CH50 and eculizumab was analyzed using generalized linear models with logistic link function. Suboptimal eculizumab concentrations (< 35 µg/ml) were reported in 5% of the samples. Furthermore, CH50 measured in these patients (median follow-up of 13 months, with a minimum of 6 months of treatment) showed a CH50 > 10% in 49% of patients prior to the next eculizumab administration. Complete blockade of complement (CH50 < 10%) was associated with lower LDH levels (longitudinal Tobit regression model). An increase in CH50 by 1.4% per 100 U/L (95% CI 0.03–2.7) increase of LDH was observed. All patients with eculizumab serum levels > 150 µg/ml did not experience breakthrough hemolysis [55].

4.2.2 Atypical Hemolytic Uremic Syndrome

To analyze the efficacy of eculizumab in aHUS, free C5 is used as a read-out. In both prospective studies (C08-002 and

C08-003), a median reduction of 50 and 62%, respectively, was observed in C5 activity, and eculizumab C_{trough} levels $> 50 \mu\text{g/ml}$ correlated with a decrease in free C5 by $> 90\%$ [56]. CH50 levels were either reduced or were undetectable after 7 days of therapy [56]. After 24 weeks, complete inhibition of complement activity was reported in all participants; however, no specific values were reported regarding complement activation and eculizumab concentrations [6, 75]. A prospective study in pediatric aHUS patients (C10-003) did not report complement inhibition data, only that all patients showed signs indicative of complement inhibition after 24 h [60].

Gatault et al. described a concentration–effect relationship in seven aHUS patients and two PNH patients treated with eculizumab. With the regression technique ($A = 20.6 \times \exp(-0.083 \times C)$), the relation between hemolytic activity and PK was described. No lysis was detected when C_{trough} levels were $> 20 \mu\text{g/ml}$, using a CH50 SPAPLUS kit that measures liposome lysis. However, Gatault et al. state that this assay is less sensitive and is hence not recommended. They also used an ELISA kit to measure C9, to detect low to moderate depression of complement activity that corresponds with CH50. Complement activity was detected with this assay when C_{trough} levels were $< 59 \mu\text{g/ml}$ [9].

4.2.3 Other Populations

Jodele et al. described the correlation–effect relationship between eculizumab concentrations and CH50 levels in 365 paired samples of 18 patients with HSCT-TMA [18]. The eculizumab concentration necessary to fully block complement activation ($\text{CH50} < 10\%$) was determined with a receiver operating characteristic (ROC) curve to maximize the Youden's Index (specificity + sensitivity – 1). Eculizumab levels $> 99 \mu\text{g/ml}$ were associated with a suppressed CH50 [18]. PD data are sporadically reported for gMG. An EMA assessment report describes the population PK/PD analysis, with free C5 as the target engagement and hemolytic activity for proof of pharmacology [5].

5 Covariates for Eculizumab PD

In some patients with PNH or aHUS, a suboptimal (defined as persistent disease activity) response to eculizumab is described despite adequate eculizumab concentrations and suppression of CH50. Various potential mechanisms have been proposed to explain this phenomenon. Although CH50 is suppressed, sC5b-C9 levels can remain elevated, indicating ongoing complement activation. Another possibility could be the decreased CL of sC5b-C9 complexes due to the binding of eculizumab to C5b [71].

In patients with PNH, long-term studies revealed breakthrough hemolysis during maintenance therapy, and half of all patients had insufficient blockage of complement prior to the next infusion [55]. Different etiologies could be the cause of this ongoing hemolysis. The most prominent etiologies are considered to be C3 opsonization of erythrocytes, making them more vulnerable to hemolysis, and insufficient C5 blockage by either inadequate C_{trough} levels or in case of strong complement activation [76, 77]. Multiple studies have described ex vivo detection of hemolytic activity, indicating ongoing complement activation, despite eculizumab treatment with adequate C_{trough} levels. Besides discordant results between different assays used in the clinics, remaining hemolytic activity could persist in light of strong complement activation [76]. Careful characterization and monitoring of these patients is necessary to understand this mechanism [76].

Nishimura et al. described 11 PNH patients (3.2% of the PNH population receiving eculizumab) with a poor response to eculizumab [78]. Despite adequate C_{max} and C_{trough} concentrations, patients had ongoing hemolysis, and all had a single missense C5 heterozygous sequence variant c.2654G → A, which corresponds to the polymorphism p.Arg885His. This genetic variant prohibits the binding of eculizumab to C5, and subsequently C5 capacity to form the lytic C5b-C9 remains present. Further screening revealed the same prevalence of this variant among healthy controls in Japan [78]. Separately, an Asian PNH patient with poor response to eculizumab had a c.2653C → T mutation in C5, which predicts p.Arg885Cys. Both mutations were not found in a cohort of 220 Chinese PNH patients and 259 healthy controls [79]. Schatz-Jakobsen et al. investigated the structural changes in C5 as a consequence of these mutations. Due to the replacement of arginine by histidine or cysteine, the arginine-binding pocket is too small and hence eculizumab cannot bind to C5 [80].

5.1 Incremental Value of Therapeutic Drug Monitoring of Eculizumab Therapy

We have reviewed the basic pharmacology of eculizumab in all diseases for which this drug is currently licensed. Next, we described the PK and PK–PD relations, as well as covariates that impact both the PK and PD. Striking is the high interindividual variation. We advocate for an individualized approach to provide the best tailored care.

We hypothesize that by performing therapeutic drug monitoring (TDM), one could adjust the dose and/or dosing intervals and thereby maximize treatment response and reduce treatment costs. As an illustration, we performed a simulation study of the effect of TDM of eculizumab in PNH patients. We simulated a population of 1000 virtual adult patients based on the population PK and PD of eculizumab in PNH patients as described by the pharmaceutical company, with an average body weight of 70 kg

(20% variation) [73]. After simulation of the virtual individuals, the individual PK parameters for each individual were used to predict the steady-state exposure after dose adaptation. We simulated the PK of eculizumab at steady state (after 8 weeks of standard treatment, including the induction phase) and applied a protocol for TDM based on the measurement of the steady state C_{trough} , using the following algorithm: the absolute dose at each administration (900 mg) remained the same, but the dosing interval was adjusted, based on the measured C_{trough} levels. When C_{trough} levels were below the target of 30 $\mu\text{g}/\text{ml}$, we decreased the dosing interval from 2 weeks to 1 week. When the C_{trough} was between 30 and 90 $\mu\text{g}/\text{ml}$, the usual 2-week interval was maintained. At higher exposure, the dosing intervals were extended: a C_{trough} of 90–120 resulted in a 3-week dosing interval, a C_{trough} between 120 and 210 $\mu\text{g}/\text{ml}$ resulted in a 4-week interval, and a $C_{\text{trough}} > 210$ $\mu\text{g}/\text{ml}$ resulted in an interval of 5 weeks. The results of the simulation are presented in Fig. 2, where the predicted C_{trough} and associated inhibition of C5 activity are shown before and after the TDM intervention. Without TDM, large inter-individual variation in predicted exposure can be observed, with a median C_{trough} level of 76 $\mu\text{g}/\text{ml}$ (range 4–362) when using the standard dose regimen. By using TDM, median C_{trough} levels decrease to 58 $\mu\text{g}/\text{ml}$ (range 30–131) [Fig. 2a]. Furthermore, simultaneously with decreasing the range of C_{trough} levels, a decrease in the variation of C5 inhibition could be observed, with more patients reaching target

attainment (Fig. 2b). Moreover, with our TDM regimen, an overall cost reduction of 11% in 1000 simulated patients was achieved by diminishing eculizumab administrations. We calculated the costs of eculizumab administrations alone per patient for 1 year of treatment and compared this with standard treatment (patients who are treated for 1 year according to the treatment scheme described in Table 2). Every patient received 8 weeks of standard therapy, after which TDM was applied with adjustment of the interval between eculizumab administrations. Costs largely depend on the cumulative dose per patient, ranging from €211,618 per patient per year with a 5-weekly interval, to €726,524 per patient per year with a 1-weekly interval.

Of note, studies reporting TDM in patients with aHUS and HSCT-TMA have increased substantially [9, 10, 18, 52]. However, remarkable is the lack of studies regarding TDM in patients with PNH. Future studies should give more insight into the possibility and potential risks of TDM in patients with PNH.

In conclusion, we would like to stress the potential of TDM for the use of eculizumab in various diseases. To fully determine the efficacy of therapy, we advise monitoring both eculizumab serum levels and complement blockade by CH50. One could argue that eculizumab levels alone would be sufficient since there seems to be a clear correlation between C_{trough} and complement blockade. In our opinion, CH50 is especially important in the case of clinical deterioration despite adequate exposure.

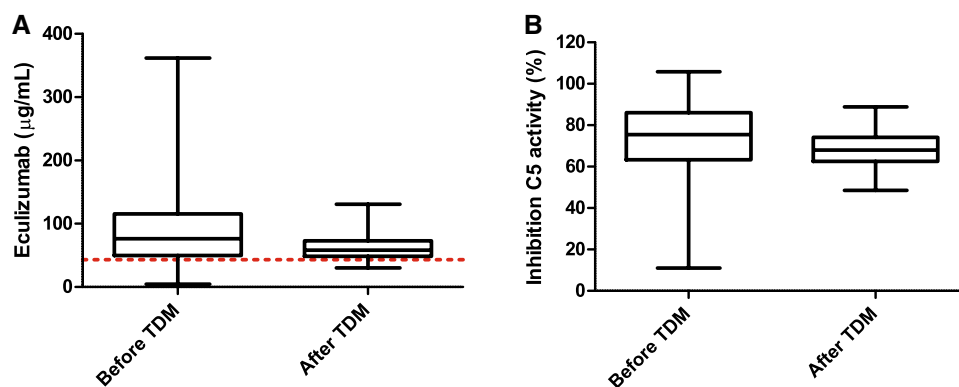


Fig. 2 Effect of TDM in PNH. TDM can guide therapy adjustments. We simulated 1000 PNH patients and assessed the pharmacokinetics of eculizumab at steady state (after 8 weeks of standard treatment, including the induction phase) and applied a protocol for TDM based on the measurement of the steady-state C_{trough} , using the following algorithm: the absolute dose at each administration (900 mg) remained the same, but the dosing interval was adjusted, based on the measured C_{trough} levels. When C_{trough} levels were below the target of 30 $\mu\text{g}/\text{ml}$, we decreased the dosing interval from 2 weeks to 1 week. When the C_{trough} was between 30 and 90 $\mu\text{g}/\text{ml}$, the usual 2-week interval was maintained. At higher exposure, the dosing intervals were extended: a C_{trough} of 90–120 resulted in a 3-week dosing inter-

val, a C_{trough} between 120 and 210 $\mu\text{g}/\text{ml}$ resulted in a 4-week interval, and a $C_{\text{trough}} > 210$ $\mu\text{g}/\text{ml}$ resulted in an interval of 5 weeks. Large variations are observed in C_{trough} levels when simulated in 1000 PNH patients according to the compartment model, as described by the pharmaceutical company. (a) A substantial number of patients do not reach the target of 35 $\mu\text{g}/\text{ml}$ (red dotted line), and, in contrast, some patients reach C_{trough} levels up to 362 $\mu\text{g}/\text{ml}$. (b) By applying TDM, the distribution can be largely diminished, with almost all patients reaching target attainment and adequate inhibition of C5 activity, as measured by serum complement hemolytic activity. TDM therapeutic drug monitoring, PNH paroxysmal nocturnal hemoglobinuria, C_{trough} trough concentration

6 Discussion

Eculizumab is known to be one of the most expensive orphan drugs worldwide. Despite multiple studies in various patient populations, little is known regarding the potential for TDM in patients receiving eculizumab. In this review, we extensively discussed the PK and PD parameters in various patient populations treated with eculizumab (PNH, aHUS, gMG, and HSCT-TMA). Furthermore, strategies to target optimal C_{trough} levels via TDM by preserving adequate complement blockade are discussed.

Although CH50 is used as a PD outcome in most of the articles, one should realize the high diversity in the assays used. Taken together with the uncertain concentration of both the bound and unbound proportion of eculizumab measured in the assay, we would advocate setting up a close collaboration with a national reference laboratory in each country. Furthermore, the potential influence of high soluble C5b-C9 levels on eculizumab levels should be further evaluated.

Eculizumab was first approved for PNH patients, with a set C_{trough} target level of 35 $\mu\text{g/ml}$ based on multiple-dose studies performed in PNH patients. On the other hand, the determined C_{trough} target level of 50–100 $\mu\text{g/ml}$ in aHUS patients is based on assumptions rather than on PK modeling. Taking into account the breakthrough hemolysis in PNH patients with a C_{trough} of 35 $\mu\text{g/ml}$, and the risks of ongoing TMA in aHUS patients, the C_{trough} target was set at 50–100 $\mu\text{g/ml}$. Especially in patients with aHUS, the duration of eculizumab treatment is a highly debated topic. Important to note is the trend towards the withdrawal of eculizumab in patients with aHUS and to only reinstitute treatment at the recurrence of disease [34, 81, 82]. Of note, most studies focused on complete complement blockade to prevent ongoing disease activity; however, it is unknown if complete blockage is necessary to prevent disease progression in the acute and/or remission phase. Ardissino et al. recently described eculizumab treatment in aHUS patients with impaired instead of fully blocked complement activity [83]. With CH50 < 30% instead of completely suppressed, no recurrences were observed.

Eculizumab has only recently been approved for the treatment of gMG. Striking is the lack of data correlating complement inhibition to clinical deterioration in patients with gMG. Furthermore, no relation between eculizumab concentration and the primary efficacy endpoint was seen; hence, monitoring complement inhibition while receiving eculizumab therapy needs to be evaluated. Future (extension) studies should provide more data regarding eculizumab treatment in gMG. Since IVIGs are used as therapy in gMG, one should realize that eculizumab C_{trough} levels

could therefore be influenced. During trials, patients had a washout period before receiving eculizumab.

Since the introduction of eculizumab as a first complement inhibitor, many trials have been conducted to study the effect of improved and alternative complement inhibitors. Phase III trials are currently being conducted to study the long-acting variant of eculizumab—ravulizumab—in patients with PNH and aHUS [84, 85]. In addition to drugs targeting C5, many other components of the complement system have been proposed as a target to halt complement activation. Various complement-targeted drugs have reached late-stage clinical trial development [4], however until now, eculizumab remains the gold-standard treatment for patients with PNH and aHUS.

7 Conclusions

To minimize unnecessary use of the highly expensive orphan drug eculizumab, and to assess the optimal treatment scheme, TDM may be performed using eculizumab C_{trough} levels. Furthermore, disease activity should be monitored to look for possibilities to taper treatment. Treatment algorithms should be developed to explore the possibility of individual dosing regimens based on set C_{trough} levels, together with CH50.

Compliance with Ethical Standards

Funding This work was supported by grants from ZonMw ‘Goed Gebruik Geneesmiddelen’ (Project number 836031008) and the Dutch Kidney Foundation (13O1116). These organizations did not have any role in drafting this manuscript or the decision to submit the manuscript for publication.

Conflicts of interest Dr. Nicole C.A.J. van de Kar and Prof. Dr. Jack F.M. Wetzels are both members of the international advisory board of Alexion, and Prof. Dr. Jack F.M. Wetzels also received a grant from Alexion. Roger J. Brüggemann has served as a consultant to Astellas Pharma, Inc., F2G, Gilead Sciences, Merck Sharpe and Dome Corp., and Pfizer, Inc., and has received unrestricted research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharpe and Dome Corp., and Pfizer, Inc. All contracts were through Radboud University Medical Center (Radboudumc) and all payments were invoiced by Radboudumc. Kioa L. Wijnsma, Rob ter Heine, Dirk Jan A.R. Moes, Saskia Langemeijer, Saskia E.M. Schols, Elena B. Volokhina and Lambertus P. van den Heuvel have no conflict of interest.

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