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EDITORIAL

Optimal duration of treatment with eculizumab in atypical hemolytic uremic syndrome (aHUS)—a question to be addressed in a scientific way

Gema Ariceta [1]

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Introduction

Atypical hemolytic uremic syndrome (aHUS) is an ultrarare disease caused, in most cases, by dysregulation of the alternative complement (C′) pathway at the surface of the vascular endothelium [1–3]. Uncontrolled C′ activation due to genetic abnormalities of several regulatory proteins, such as complement factor H (FH) [4–13] or auto-antibodies against FH synthesis [14, 15], lead to increased C3 convertase production and/or reduced degradation [16], which in turn result in excessive C5 activation, C5b-9 formation (also named terminal complement complex (TCC)), and subsequently endothelial cell lysis [17, 18]. Independent of the individual specific C′ anomaly, aHUS is a disease driven by a common pathogenic mechanism: C5 activation [19, 20].

Affected patients are vulnerable to C′ pathway stimulus and exhibit excessive C3b deposits on the surface of the endothelium membrane [16, 21]. Incomplete penetrance (~ 50%) of aHUS in mutation carriers is common. Concurrent environmental agents, commonly infections, or additional endothelial damaging factors, will further amplify C′ activation and trigger the disease due to impaired protection of microvasculature cells to C′ injury [22]. The course of the disease is characterized by relapses separated by remission periods, both often preceded by external factors [1, 17–19]. It is generally accepted that individual predisposition to aHUS results from the combination of different inherited and environmental factors [22, 23].

Atypical hemolytic uremic syndrome is a disease characterized by thrombotic microangiopathy (TMA) which is defined by the concurrent triad of non-immune microangiopathic hemolytic anemia, thrombocytopenia, and vital organ damage, most frequently the kidney [1, 17–19]. The discovery that constitutive C′ alternative pathway dysregulation at the endothelial cell membrane surfaces plays a primary role in the pathogenic mechanism for most patients with aHUS provided a robust argument in favor of therapeutic complement blockade in those patients [20, 22–25]. Eculizumab, a humanized antibody which prevents C5 convertase activation that avoids TCC formation, and resulting endothelial damage, is the first in class complement blocker drug, effective in every specific C′ anomaly in patients with aHUS [23, 24]. Eculizumab was approved by the FDA and EMA as a specific treatment for aHUS in 2011 [26, 27], after the success of four industry-sponsored prospective non-randomized trials including 100 patients (78 adults and 22 children), which demonstrated hematologic remission with normalization of platelet count within 7–8 days; lactate dehydrogenase level (LDH) after 14–54 days; and more importantly, a mean estimated glomerular filtration (eGFR) rate recovery of 64 mL/min/1.73m^2 in children and 30–35 mL/ min/1.73m^2 in adults—a time-dependent response, with a more favorable outcome in those patients who started treatment during the first week of disease [28–31]. Since then, eculizumab has become the elective treatment of patients with aHUS [23–26] based on its remarkable positive effect on hematological remission, preservation renal function in native kidneys and to a lesser extent in kidney allografts, and recovery from extra-renal manifestations [29, 30, 32], preventing disease recurrence after kidney transplantation (KTx) [33], even using selective living-related donor allografts in an individualized manner [32].

Therefore, treatment with eculizumab has changed the natural history of aHUS, substantially improving patient survival and outcome from the historic treatment with plasma exchange or infusion (PE/PI) [34, 35], a suboptimal therapy useful in the absence of eculizumab [23, 24, 34]. Prior to the availability of eculizumab, data from aHUS patient registries in different countries invariably described high rates of mortality, progression to end-stage kidney disease (ESKD), and disease recurrence risk in 60% of patients after KTx.

✉ Gema Ariceta
gariceta@vhebron.net

[1] Pediatric Nephrology, Hospital Universitari Vall d' Hebron, Universitat Autonoma de Barcelona, Barcelona, Spain

Approximately, 29 and 56% of children and adults with aHUS, respectively, progressed to ESKD or died within 1 year of disease presentation [36, 37], and those with preserved renal function suffered more relapses later on—30% within the first year and 20% of adults and 50% of children continued presenting relapses subsequently [37].

Recently, real-world data from The Global aHUS Registry demonstrated ESKD-free survival of 79 and 73% in pediatric patients with aHUS, and 69 and 51% in adult patients at 1 and 5 years, respectively, with similar outcome among different C′ abnormality statuses [38]. Further, case report descriptions have also supported the efficacy of eculizumab in recovery from systemic manifestations, such as in the central nervous system, ischemic cardiomyopathy, distal ischemia, necrotic skin lesions, and ophthalmologic involvement [22].

Since eculizumab is used as first-line therapy in children [23] and is also recommended early in the disease in adults after exclusion of other causes of TMA, mainly thrombotic thrombocytopenic purpura (TTP) [19, 22, 24], treated aHUS patients experience lack of relapses or disease activity in the long term [39]. Absence of disease activity has promoted large controversy regarding eculizumab dosing schedule and treatment duration.

Challenges in aHUS diagnosis

Overall, diagnosis of aHUS is based on patient clinical characteristics [1] due to the absence of a unique confirmatory test [2, 3]. However, the phenotypic presentation of aHUS can be very heterogeneous due to variable disease severity and systemic involvement, as well as potential overlap with other manifestations caused by external triggers that may even mask the aHUS clinical picture [19]. Laborious differential diagnosis [23, 34] and disease rarity (incidence of ~ 0.5 per million per year) illustrate the challenge of establishing an accurate differential diagnosis [24], mainly in adults with associated comorbidities [19, 20, 22].

At least 50–60% of aHUS patients have an underlying inherited and/or acquired C′ abnormality which explains the mechanism of the disease [17, 36, 37]. However, identification of a C′ gene pathogenic variant is not required for the diagnosis of aHUS [23, 39, 40]. Further, genetic analysis is complex, involves at least nine different genes (*CFH*, *CD46-MCP, CFI, C3, CFB, THBD*, *CFHR1, CFHR5*, and *DGKE*), and should also include genotyping for the risk haplotypes (CFH-CFHR3 and MCPggaac) and detection of copy number variation, hybrid genes, and other complex genomic rearrangements in the CFH/CFHRs genomic region [19, 24]. Consequently, genetic diagnosis is usually not available at the acute phase of the disease and cannot support the diagnosis of aHUS [23] but may drive long-term management of the disease [22–24]. Further, grouped data from patient registries have demonstrated there is no difference in aHUS severity between patients with or without an identified C′ gene pathogenic variant. In addition, the response to eculizumab is similar in patients with or without identified mutations [38]. An exception to this rule is the detection of anti-FH antibodies which is a useful test that not only confirms the diagnosis but indicates a specific management including immunosuppression [14, 41].

Finally, recent efforts for terminology standardization of different entities causing TMA should provide clarification and facilitate the specific diagnosis and management of different aHUS subtypes, such as complement blockade in what is named “complement-mediated HUS” [42, 43].

Eculizumab® dosing schedule and treatment duration

Eculizumab is administered by intravenous access [26, 27]. Approved prescription for aHUS in children and adults consists of an induction phase first, and later, a patient weight-based life-long maintenance dose at biweekly intervals, to target drug serum levels of 50–100 μg/ml [28–31]. However, this current standard is controversial, and the major question today is what the optimal duration of eculizumab treatment should be [24]. Patient burden associated with biweekly IV treatment is one of the arguments questioning eculizumab dosing, but the main controversies regard associated infection-risk and remarkably, cost.

Infection-risk

Administration of eculizumab prevents TCC formation, which represents the main immunity mechanism against *Neisseria meningitis*. Thus, the estimated risk of meningococcal infections in patients treated with eculizumab is 0.5% per year, a relative risk of 5000 compared to the general population, which is the same as for individuals with congenital complete deficiency in terminal C′ [23]. Vaccination against *Neisseria* serogroups A, C, W135, and Y and against serogroup B is mandatory before initiating eculizumab, but prescription of antibiotics during at least 2 weeks after vaccination avoids delaying treatment in emergency [26, 27]. The cumulative reporting rate of meningococcal infections in eculizumab-treated patients in the post-marketing setting was 0.33 per 100 patient-years (compared to 0.83 cases per 100 patient-years during clinical trials) [26]. Controversy remains regarding vaccination efficacy [24] and maintenance of antibiotic prophylaxis during the duration of eculizumab treatment [19, 23]. In case of C′ blockade interruption, antibiotics should be maintained for an additional 2–3 months [23, 24].

Cost

The annual cost of eculizumab treatment for a patient > 40 kg is ~€500,000 per year, which represents the most expensive treatment in the field of Pediatric Nephrology. Despite being a life-rescuing drug, eculizumab is unaffordable in many countries [44], or only available with specific restrictions [45]. The balance between pharmaceutical companies' economic incentives with societal budgetary constraints and the ethical imperative of timely access to expensive orphan drugs such as eculizumab is advocated [46].

Complement activity monitoring and reduced eculizumab dose

Some case reports have shown patients who remained in remission while receiving a reduced dose of eculizumab (often administered at longer intervals than approved label) or eculizumab cessation. Expert recommendations have opened the way for using lower eculizumab doses while preserving C′ blockade (measured by total complement activity or CH50 < 10% of normal, alternative pathway hemolytic activity or AH50 < 10% of normal, and eculizumab trough level 50–100 mg/ml) [24].

Following this concept, Gatault et al. developed a one-compartment model to predict pharmacokinetics and pharmacodynamics of eculizumab using the data of seven patients with aHUS and supported the extension of eculizumab infusion interval to 4 weeks in patients < 90 kg and even to 6 weeks in patients with body weight < 70 kg [47].

Since then, some reports analyzing C′ blockade in small cohorts of patients treated with prolonged intervals of eculizumab after a time on remission receiving the recommended dose have been published. Cugno et al. studied 18 aHUS patients (aged 2–40 years) treated with eculizumab in accordance with the standard scheme. Once they achieved remission, the time intervals between eculizumab infusions were progressively increased to 3 weeks and later 4 weeks, based on a patients' clinical condition and laboratory findings (haptoglobin, LDH, serum creatinine levels, platelet count, and C′ activity measured by Wieslab method—CH50, C3 antigen and C5 activity levels). Patients were strictly monitored and weekly, a urine dipstick test was used to rule out hemoglobinuria. The duration of the study was 160 months. The authors observed that C′ functional activity was completely suppressed not only 1 and 2 weeks after the last eculizumab infusion but also after 3 weeks [48].

Volokhina et al. also analyzed 5 out of 8 aHUS patients receiving prolonged intervals of eculizumab. All patient samples were completely blocked for terminal C′ pathway activity for up to 4 weeks after eculizumab administration. Further, titration of serum complexes between eculizumab and C5 levels revealed an excess of the drug up to 4 weeks after infusion in the authors' opinion, but without providing real drug quantification [49]. A short time ago, the same group of authors, this time measuring drug levels in 11 aHUS patients treated with eculizumab given at infusion intervals of 4–5 weeks, described that 80% had eculizumab trough levels > 50 μg ml and C′ fully blocked (as measured by CH50 < 10%) [50].

More recently, Ardissino et al. reported the outcome of prolonged intervals of eculizumab after 2.6 months of sustainable disease remission on the recommended drug dosing for 38 patients with aHUS (13 children). Twenty-two out of 38 patients received eculizumab every 4 weeks, and 16 out of 38 every 3 weeks, with a target of CH50 activity of < 30%. After a cumulative median observation of 1208 months, none of the patients relapsed, and a median dose of eculizumab of 0.75 mg/kg/day was administered in comparison with the label dose of the drug that recommends 1.2 mg/kg/day in a 70-kg adult and 1.6 mg/kg/day in a 40-kg child [51].

Those experiences are of great value and may help in moving from a standard and rigid eculizumab treatment scheme to a more personalized dosing approach. However, the key argument is the availability of monitoring patient C′ blockade in a timely manner. Interpretation of eculizumab levels is difficult since the assays differ from each other, and all detect both bound and unbound drug [24]. Functional assays of serum C′ activity (C3, C3d, C5, C5a, soluble C5b-C9, AP50) also provide conflicting or inconclusive results between different labs, and ex vivo endothelial cell assay—proposed as the gold-standard for aHUS activity monitoring—in practice is not available outside the research environment [21]. Further, we have limited understanding of the time course of a clinical episode of aHUS and whether disease activity persists or not [24]. Study cohorts sizes, potential center effects, limited patient follow-up, and disease pattern course characterized by remission and recurrent phases all justify caution and raise the question of generalization of those results from expert centers to general clinical practice. In addition, comparison between similar risk individuals is challenging, with mostly adult patients—who present with late onset of the disease after a robust environmental trigger—among those treated with reduced eculizumab dose, whose recurrence risk may differ from children affected by the disease from early life.

Discontinuation of eculizumab and restrictive use

There are no robust prospective controlled studies in patients with aHUS to define criteria for discontinuation of eculizumab therapy, but there are an increasing number of reports of patients who remained on remission after treatment cessation. A key question is whether patients with aHUS have alternative C′ pathway continuous hyperactivation and induced endothelial cell damage or not. Experts recommended that

discontinuation of eculizumab could be considered on a case-by-case basis in patients after at least 6 to 12 months of treatment (or after 3 months in children with pathogenic *MCP* variants) and at least 3 months of normalization (or stabilization of residual chronic kidney disease) of kidney function, excluding KTx recipients and children younger than 3 years of age [23, 24, 32].

Some isolated case reports, and recently, larger cohort descriptions, have shown that interruption of eculizumab could be feasible in some patients. Ardissino et al. reported that in 10 aHUS patients who stopped eculizumab, 3 of them—all with *CFH* pathogenic variants—experienced a relapse within 6 weeks of discontinuation but completely recovered after immediately resuming treatment [52]. In a more recent publication from the same authors describing a total of 16 patients who discontinued eculizumab, 5/16 patients (31%) also experienced a relapse, and previous renal function recovered after reintroducing eculizumab. Most relapses occurred a short time after treatment cessation. Study follow-up ranged from 0.4 to 40 months [53].

In a parallel approach, the Dutch group of Wijnsma et al. [54] described 20 patients (14 adults, 6 children) with aHUS, in whom eculizumab was tapered in all and stopped in 17 patients. aHUS recurrence occurred in 5 patients (with *CFH* or *CFB* pathogenic variants), and early detection and treatment restart prevented any clinical sequelae. In total, eculizumab was discontinued in 13 patients without aHUS recurrence, of whom 5 were event free for > 1 year.

In agreement with previous studies, data from the non-interventional Global aHUS Registry (NCT01522183) demonstrated that among 1147 aHUS patients treated with eculizumab, those who remained on treatment had a lower TMA rate than patients who discontinued treatment (3.6 versus 10.7 per 100 patient-years, respectively) [55].

Overall, the available data indicate that eculizumab discontinuation may be reasonable in patients without detected C′ gene variants. In the largest retrospective series, none of the 17 patients with no rare variant detected relapsed, and the estimated relapse-risk in that sort of patient is < 10% [56]. Conversely, 8 of 11 patients (72%) with *CFH* variants and 4 of 8 (50%) with *MCP* variants relapsed after treatment cessation. In all case reports combined, the risk of relapse after eculizumab discontinuation was 60%, 37.5%, and 43% in patients with *CFH, MCP*, and *C3* variants, respectively. In the majority of cases, fast restart of eculizumab achieved remission without additional kidney damage. No information regarding very infrequent variants is available [32]. The specific subtype of aHUS caused by auto-antibodies against FH [14, 15] represents the most appealing subtype for eculizumab interruption, but again "*real life*" experience has shown better outcome in those patients continuing treatment with eculizumab [41].

Nevertheless, there is a lack of data about the long-term impact of eculizumab discontinuation in the discussed published cohorts. A major criticism is that those studies could be biased, since eculizumab may be withdrawn in selected patients and not per protocol in all of them. The fact that in most centers extensive genetic analysis is not achievable in the short-term, as well as limited clinical experience, represents an additional challenge to following that approach.

A new strong statement in favor of a restrictive approach for eculizumab treatment in aHUS, based on the studies discussed above and our own experience [52–56], has been advocated recently [57]. Expert research on C′ and a skilled Dutch clinical group has published a restrictive therapeutic aHUS protocol based on patient age, C′ gene variant profile, and coordination by a national referent center, to provide distinct eculizumab treatment patterns in terms of duration, full or reduced dose, and complete or partial C′ activity blockade [57]. Unfortunately, the outcome of that approach is still unknown as a prospective observational national monitoring project (CUREiHUS, NTR5988) to guide eculizumab therapy in aHUS is ongoing.

Finally, the proposed restrictive approach in aHUS in adult transplant patients or in adult candidates for KTx [57] is highly questionable due to controversial results, limited recovery after eculizumab resumption, and lack of alignment with expert recommendations [22–24, 33]. New information from the Global aHUS Registry analyzing the outcome of 188 KTx patients with at least 1 year of follow-up after their most recent transplant demonstrated significantly better 2-year eGFR (70.2 ml/min/1.73m^2) in the subgroup of patients receiving eculizumab beginning at the time of transplantation in comparison with the subgroup receiving eculizumab after KTx with a previous diagnosis of aHUS (44.8 ml/min/1.73m^2) or the subgroup diagnosed with aHUS and treated after KTx (24.2 ml/min/1.73m^2) [58].

Conclusion

Treatment with eculizumab has changed the natural history of complement-mediated HUS. Originally approved for long-life treatment, clinical experience from highly expert centers support moving from a fixed treatment schedule to a personalized dosing, at least in selected patients. Limitations in disease-monitoring tools, and in genetic diagnosis in regular clinical practice, question the generalization of that approach. The balance between the ethical obligation to offer patients the best treatment, drug affordability, and patient risk requires a strict and rigorous prospective international research collaborative effort to provide proof and guidelines for aHUS future management.

Compliance with ethical standards

Conflict of interest GA has received lecture and advisory honoraria from Alexion Pharmaceuticals and is a member of the Scientific Advisory Board of the Global aHUS Registry sponsored by Alexion Pharmaceuticals.

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