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Editorial Comment

EDITORIAL COMMENT

Should eculizumab be discontinued in patients with atypical hemolytic uremic syndrome?

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Abstract

Atypical hemolytic uremic syndrome (aHUS) is a life-threatening disorder for which prompt diagnosis and eculizumab treatment is indicated. The time for relapse and patients at risk for relapse after eculizumab discontinuation are unknown. While some authors believe there is no clinical evidence supporting eculizumab discontinuation, which may be associated with high collateral risks such as loss of renal function, other authors believe that the drug can be safely discontinued with close patient monitoring. In this editorial, we update the pros and cons for eculizumab discontinuation in aHUS.

Atypical hemolytic uremic syndrome (aHUS) is a rare and life-threatening disease caused, in the majority of cases, by uncontrolled complement activation. aHUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. The histologic lesions of aHUS are characterized by the thickening of arterioles and capillaries, endothelial swelling and detachment, thrombosis and obstruction of the vessel lumina, namely thrombotic microangiopathy (TMA) [1–3]. These lesions mainly affect the kidney, which is particularly vulnerable to complement-mediated inflammatory injury. Other organs such as the brain, heart, lungs, eyes, gastrointestinal tract, liver and pancreas might also be affected [1–3].

Eculizumab is approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of aHUS and has dramatically improved the outcome of aHUS. Eculizumab is a humanized monoclonal antibody that blocks the cleavage of terminal complement protein C5 into the inflammatory C5a protein and C5b, a precursor of the lytic C5b-9 complex [4–11]. Before eculizumab was approved, the prognosis for patients with aHUS was poor: up to 79% of patients died, required dialysis or had permanent renal damage within 3 years of diagnosis [2]. Now, the majority of patients (73%) with aHUS reach complete TMA response, with improvements in hematologic and kidney disease outcomes at 26 weeks after initiation of eculizumab therapy [12]. Thus, eculizumab is a highly effective, but expensive, therapy that has improved the outcome of patients with aHUS. A prompt and accurate diagnosis of aHUS can be life saving if eculizumab treatment is promptly initiated. Current guidelines recommend chronic eculizumab treatment for patients displaying a positive response. However, the optimal duration of eculizumab treatment in aHUS is unknown [13, 14].

Discontinuing eculizumab therapy has been previously described in very limited experiences, with inconclusive results. The main rationale for discontinuing eculizumab therapy was to protect patients from the risk of potentially devastating side effects, such as meningococcal infection, and the expensive cost of the drug. In this regard, the experience of Ardissino *et al.* [15, 16] supports the possibility of discontinuing eculizumab treatment in patients in stable remission, but this decision may depend on the identified gene mutation, patient commitment and strict patient monitoring.

The Global aHUS Registry is the largest registry of the disease by number of enrolled patients, and recently assessed eculizumab treatment, discontinuation and reinitiation. Data from

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the registry show that among 406 patients enrolled from 13 countries, 235 (57.9%) patients received eculizumab for a mean duration of 0.4 years, 46 (20%) patients discontinued eculizumab and 5 (10%) restarted the drug. New data from the Global aHUS Registry will be of great interest for evaluating aHUS evolution [17, 18]. In this issue of *Clinical Kidney Journal*, Macia *et al.* [19] analysed available data for the medical evaluation of eculizumab discontinuation and TMA risk. Patients with aHUS who discontinued eculizumab treatment were identified from different sources: (i) case studies (published in English) of patients with aHUS who discontinued eculizumab, including six unpublished cases from the authors' clinics; (ii) data from prospective and retrospective clinical trials including long-term follow-up studies and (iii) the Global aHUS Registry. The authors conclude that discontinuation of eculizumab may increase the risk of further clinical manifestations of TMA, accompanied by more severe damage in target organs, such as renal function loss. In addition, they pointed out that functional tests of complement activity and complement protein levels do not provide reliable data for predicting an aHUS flare. Thus, novel strategies for monitoring complement activation and aHUS activity, particularly for identifying ongoing subclinical TMA, are needed and should be developed [19].

Recently, Fakhouri *et al.* [20] studied a 2-year experience with eculizumab discontinuation in patients with aHUS from the French Registry database. They retrospectively identified all dialysis-free patients with aHUS who discontinued eculizumab between 2010 and 2014 and reviewed their clinical and biologic parameters. The decision to discontinue eculizumab was made by the clinician in charge of the patient. Patients were closely monitored by regular urine dipsticks and blood tests, and the treatment was rapidly restarted in case of relapse. They found that among 108 patients treated with eculizumab, 38 patients (9 children and 29 adults) discontinued the drug after a median time under treatment of 17.5 months. Twenty-one patients (55%) carried novel or rare complement gene variants. Renal recovery under eculizumab was equally good in all patients. Twelve patients (31%) experienced aHUS relapse. Eight of 11 patients (72%) with complement factor H variants, 4 of 8 patients (50%) with membrane cofactor protein (MCP) variants and none of 16 patients without rare complement gene variants relapsed. In relapsing patients, early eculizumab reintroduction led to rapid (<7 days) hematologic remission and a return of serum creatinine to baseline levels. At the last follow-up, renal function remained unchanged in non-relapsing and relapsing patients compared with baseline values before eculizumab discontinuation. This study suggests that pathogenic variants in complement genes are associated with a higher risk of aHUS relapse after treatment discontinuation, but discontinuation of eculizumab in patients without rare complement gene variants may be safer.

In conclusion, the study by Macia *et al.* [19] demonstrates that discontinuation of eculizumab may increase the risk of further clinical manifestations of TMA. Thus, the authors suggest that until tools are available to provide more robust risk stratification and adequately monitor complement activation and disease activity, eculizumab discontinuation will not be an evidence-based decision. In contrast, other authors experience and publications support the possibility of safely discontinuing eculizumab therapy with strict home monitoring for early signs of relapse in patients with aHUS. In addition, pathogenic variants in complement genes were associated with a higher risk of aHUS relapse after eculizumab discontinuation. Further studies are needed to identify aHUS patients at risk of relapse and delineate the best therapeutic strategy in those patients. In addition, information from larger data sets, such as the Global aHUS Registry (ClinicalTrials.gov, NCT01522183) and the EVIDENCE study (NCT02614898), will help clinicians to better estimate the probability of relapse and make the most appropriate individualized decisions.

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Conflict of Interest Statement

None declared.

References

1. Noris M, Remuzzi G. Cardiovascular complications in atypical haemolytic uraemic syndrome. *Nat Rev Nephrol* 2014; 10: 174–180
2. Noris M, Caprioli J, Bresin E *et al.* Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol* 2010; 5: 1844–1859
3. Noris M, Remuzzi G. Atypical hemolytic–uremic syndrome. *N Engl J Med* 2009; 361: 1676–1687
4. Cofiell R, Kukreja A, Bedard K *et al.* Eculizumab reduces complement activation, inflammation, endothelial damage, thrombosis, and renal injury markers in aHUS. *Blood* 2015; 125: 3253–3262
5. Kim JJ, Waller SC, Reid CJ. Eculizumab in atypical haemolytic-uraemic syndrome allows cessation of plasma exchange and dialysis. *Clin Kidney J* 2012; 5: 34–36
6. Garjau M, Azancot M, Ramos R *et al.* Early treatment with eculizumab in atypical haemolytic uraemic syndrome. *Clin Kidney J* 2012; 5: 31–33
7. Fremeaux-Bacchi V. Treatment of atypical uraemic syndrome in the era of eculizumab. *Clin Kidney J* 2012; 5: 4–6
8. Greenbaum LA, Fila M, Ardissino G *et al.* Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome. *Kidney Int* 2016; 89: 701–711
9. Legendre CM, Licht C, Loirat C. Eculizumab in atypical hemolytic–uremic syndrome. *N Engl J Med* 2013; 369: 1377–1380
10. Licht C, Greenbaum LA, Muus P *et al.* Efficacy and safety of eculizumab in atypical hemolytic uremic syndrome from 2-year extensions of phase 2 studies. *Kidney Int* 2015; 87: 1061–1073
11. Legendre CM, Licht C, Muus P *et al.* Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med* 2013; 368: 2169–2181
12. Fakhouri F, Hourmant M, Campistol JM *et al.* Terminal complement inhibitor eculizumab in adult patients with atypical hemolytic uremic syndrome: a single-arm, open-label trial. *Am J Kidney Dis* 2016; 68: 84–93
13. Campistol JM, Arias M, Ariceta G *et al.* An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia* 2013; 33: 27–45
14. Campistol JM, Arias M, Ariceta G *et al.* An update for atypical haemolytic uraemic syndrome: diagnosis and treatment. A consensus document. *Nefrologia* 2015; 35: 421–447

15. Ardissino G, Possenti I, Tel F *et al*. Discontinuation of eculizumab treatment in atypical hemolytic uremic syndrome: an update. *Am J Kidney Dis* 2015; 66: 172–173
16. Ardissino G, Testa S, Possenti I *et al*. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. *Am J Kidney Dis* 2014; 64: 633–637
17. Licht C, Ardissino G, Ariceta G *et al*. The global aHUS registry: methodology and initial patient characteristics. *BMC Nephrol* 2015; 16: 207
18. Licht C, Ardissino G, Ariceta G *et al*. Characteristics of 521 adult and pediatric patients in the Global aHUS Registry. Presented at the American Society of Nephrology (ASN) Kidney Week 2014 Annual Meeting, Philadelphia, Pennsylvania, November 11–16, 2014, Poster SA-PO510
19. Macia M, Moreno FA, Dutt T *et al*. Current evidence on the discontinuation of eculizumab 1 in patients 2 with atypical haemolytic uraemic syndrome. *Clin Kidney J* 2017, (in press)
20. Fakhouri F, Fila M, Provôt F *et al*. Pathogenic variants in complement genes and risk of atypical hemolytic uremic syndrome relapse after eculizumab discontinuation. *Clin J Am Soc Nephrol* 2017; 12: 50–59