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PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology
Manuscript NO: 35013
Title: Atypical hemolytic-uremic syndrome due to complement factor I mutation
Reviewer's code: 00503255
Reviewer's country: Japan
Science editor: Li-Jun Cui
Date sent for review: 2017-08-10
Date reviewed: 2017-08-13

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

COMMENTS TO AUTHORS

The authors described a patient with atypical hemolytic uremic syndrome (aHUS) due to heterozygous CFI mutation, who was successfully treated with eculizmab and could stop the therapy. The paper is well-written and has interesting findings. 1. Some studies reported clinical outcome of aHUS with discontinuation of eculizmab. The authors should discuss this point with literature review.

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Authors' response to reviewer ID 00503255

We did literature review on cases reporting eculizumab discontinuation and added few more citations. These included case reports, case series and cases from previous eculizumab clinical trials. The following paragraphs are added to the manuscript and are written in green color. Page 12-14

Similar to our patient, several cases of eculizumab discontinuation had been described. The largest case series reported the development of TMA in 5 (31%) of 16 patients following discontinuation[35, 36]. Those patients had received eculizumab for a median of 4.3 (range, 0.5-14.4) months. In those 5 patients, relapse was identified, using regular home urine dipstick testing, within 6 months of the last eculizumab dose. Eculizumab therapy was restarted, and it resulted in rapid improvement in serum creatinine levels and proteinuria.

In an attempt to address the possibility and safety of eculizumab discontinuation, Macia *et al*[37] studied the demographics, disease characteristics, and outcomes of aHUS cases in whom eculizumab was discontinued. The post-discontinuation follow-up ranged from few days to 17 months. According to the data collected from cases reports, TMA developed in 16 (31%) of 52 cases who discontinued the drug after multiple doses and in 4 (80%) of 5 cases who discontinued the drug after a single dose. TMA development was found to be higher with a single dose of eculizumab, and hence, current evidence does not support single-dose eculizumab.

According to the data collected from eculizumab clinical trials, TMA developed in 12 (20%) of 61 patients during a median post-discontinuation follow-up of 24 weeks[37]. The median time to TMA development was 13 (range, 4-127) weeks. Three patients progressed to ESRD. The authors compared patients who experienced relapse (n=12) to those who did not (n=49) post-discontinuation across several demographic and disease characteristics. No particular trend to predict TMA development was noted with regard to sex, identified complement mutation or antibody, time from diagnosis to start of eculizumab, duration on eculizumab treatment, kidney function and dialysis (at the time of initial treatment and discontinuation), and kidney status (native versus transplant)[37]. However,

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compared with patients who experienced no relapse, there was a trend to a lower median age (19.5 vs. 27 years) and a higher proportion of CFH mutation (42% vs. 18%) among those who experienced relapse. It had been noted that the use of functional tests of complement activity and measurement of complement proteins to predict development of TMA is of limited value[37]. The authors concluded that the development of TMA following eculizumab discontinuation is unpredictable.

To our knowledge, this is the first case of aHUS due to heterozygous *CFI* variant *c.944G>A (p.Arg315Lys)* reported in Saudi Arabia. Several lessons can be learned from our case and similar cases. Although rarely reported, it is important to keep a high index of suspicion for such severe disease when acute kidney injury presents with unexplained microangiopathic anemia. In such presentations, the severity of renal disease, lack of significant neurologic symptoms, and absence of diarrhea make aHUS the likely clinical diagnosis. In addition, a renal benefit with discontinuation of dialysis was possible in our case despite relatively late initiation of eculizumab and prolonged period of dialysis-dependent kidney disease. Lastly, although eculizumab discontinuation was possible in our patient and seems to be safe in some other reported cases during the reported follow-up periods, predicting the risk of TMA development remains difficult. Therefore, informed decision-making requires a more comprehensive collection of data on eculizumab discontinuation and finding a more sensitive tool to monitor complement activation and disease activity.

New References were added to the manuscript and written in green color. Page 21-22

35. **Ardissino G**, Possenti I, Tel F, Testa S, Salardi S, Ladisa V. Discontinuation of eculizumab treatment in atypical hemolytic uremic syndrome: an update. *Am J Kidney Dis* 2015; **66**: 172-173 [PMID: 26111906 DOI: 10.1053/j.ajkd.2015.04.010]

36. **Ardissino G**, Testa S, Possenti I, Tel F, Paglialonga F, Salardi S, Tedeschi S, Belingheri M, Cugno M. Discontinuation of eculizumab maintenance treatment for atypical hemolytic uremic syndrome: a report of 10 cases. *Am J Kidney Dis* 2014; **64**: 633-737 [PMID: 24656451 DOI: 10.1053/j.ajkd.2014.01.434]

37. **Macia M**, de Alvaro Moreno F, Dutt T, Fehrman I, Hadaya K, Gasteyger C, et al. Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic uraemic syndrome. *Clin Kidney J* 2017; **10**: 310-319 [PMID: 28621343 DOI: 10.1093/ckj/sfw115]

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PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology
Manuscript NO: 35013
Title: Atypical hemolytic-uremic syndrome due to complement factor I mutation
Reviewer's code: 00503014
Reviewer's country: Taiwan
Science editor: Li-Jun Cui
Date sent for review: 2017-08-07
Date reviewed: 2017-08-16

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[Y] High priority for publication
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[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

COMMENTS TO AUTHORS

In general, the draft is an important issue and had been well-written. Only smll cooments for the authors: 1.For easy reading, the author could re-write the timeline to figure and including the renal function change.

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Authors' response to reviewer ID 00503014

We have converted the timeline table into the following figure (named Figure 2).

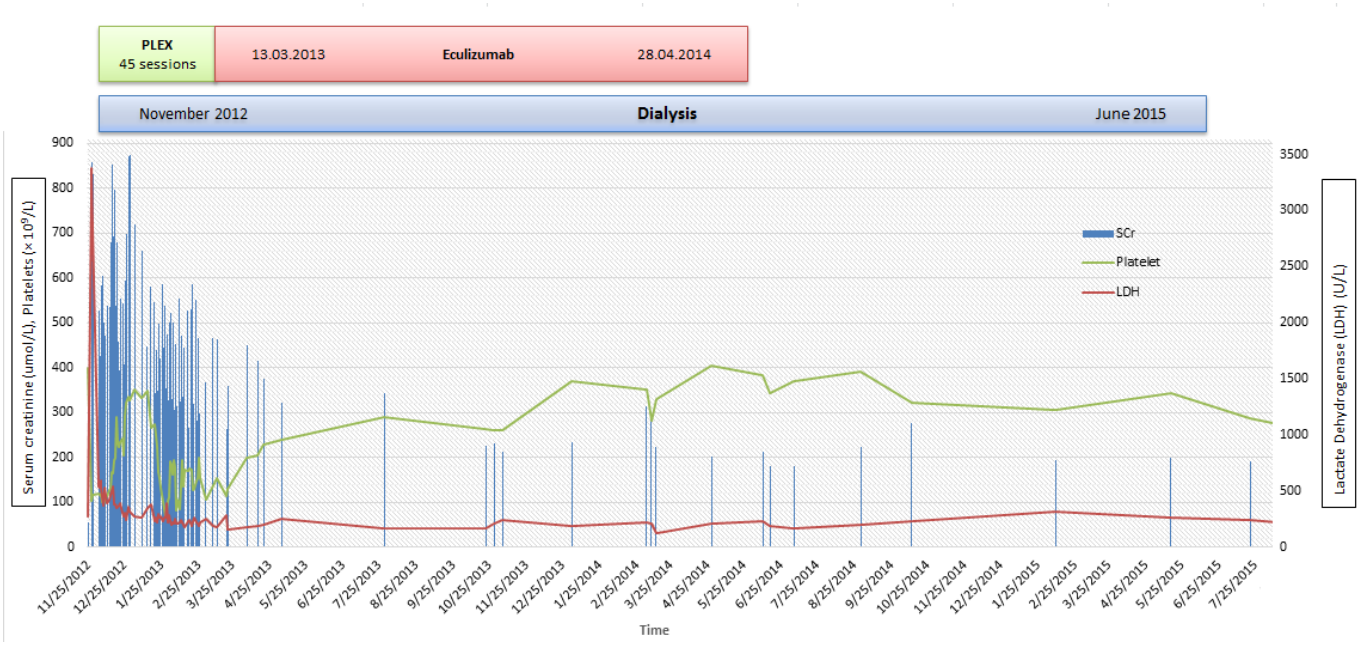

Figure 2. Serum creatinine levels did not improve despite plasma exchange, and hemodialysis was initiated. Lactate dehydrogenase levels improved with plasma exchange, whereas the platelets showed transient improvement under the plasma exchange treatment. Treatment with eculizumab induced a persistent improvement in platelet count. Continued eculizumab treatment resulted in late renal benefit, with dialysis withdrawn in June 2015. PLEX: plasma exchange; Scr: serum creatinine; LDH: lactate dehydrogenase.