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ORIGINAL ARTICLE

Current evidence on the discontinuation of eculizumab in patients with atypical haemolytic uraemic syndrome

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Abstract

Background. Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening disorder for which eculizumab is the only approved treatment. Life-long treatment is indicated; however, eculizumab discontinuation has been reported.

Methods. Unpublished authors' cases and published cases of eculizumab discontinuation are reviewed. We also report eculizumab discontinuation data from five clinical trials, plus long-term extensions and the global aHUS Registry.

Results. Of six unpublished authors' cases, four patients had a subsequent thrombotic microangiopathy (TMA) manifestation within 12 months of discontinuation. Case reports of 52 patients discontinuing eculizumab were identified; 16 (31%) had a subsequent TMA manifestation. In eculizumab clinical trials, 61/130 patients discontinued treatment between 2008 and 2015. Median follow-up post-discontinuation was 24 weeks and during this time 12 patients experienced 15 severe TMA complications and 9 of the 12 patients restarted eculizumab. TMA complications occurred irrespective of identified genetic mutation, high risk polymorphism or auto-antibody. In the global aHUS Registry, 76/296 patients (26%) discontinued, 12 (16%) of whom restarted.

Conclusions. The currently available evidence suggests TMA manifestations following discontinuation are unpredictable in both severity and timing. For evidence-based decision making, better risk stratification and valid monitoring strategies are required. Until these exist, the risk versus benefit of eculizumab discontinuation, either in specific clinical situations or at selected time points, should include consideration of the risk of further TMA manifestations.

Key words: atypical haemolytic uraemic syndrome, discontinuation, eculizumab, recurrence, thrombotic microangiopathy

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Introduction

Atypical haemolytic uraemic syndrome (aHUS) is a rare, life-threatening disorder caused, in the majority of cases, by uncontrolled complement activation [1]. This results in endothelial injury and platelet activation presenting as thrombotic microangiopathy (TMA), ischaemia and systemic end organ involvement [1–3]. Manifestation of disease requires an inherent predisposition, i.e. a genetically determined or acquired dysfunction in complement regulation, and a condition or event that initiates complement amplification, such as bacterial or viral infections, drugs, associated diseases, transplantation and, in women, pregnancy [1, 3]. The clinical course of aHUS can be both acute and severe, or almost subclinical and progressive. Historically, up to 67% of patients died or had end-stage renal disease (ESRD) within 3 years of diagnosis [4].

A paradigm shift in the management of aHUS has occurred with the availability of eculizumab, a monoclonal antibody that specifically binds to the terminal complement protein C5. Eculizumab blocks cleavage of C5–C5a (a potent anaphylatoxin) and C5b, inhibiting progression of the terminal complement pathway to the membrane attack complex, but leaving proximal complement functions intact. Eculizumab is currently the only approved treatment for aHUS [5].

Prospective clinical trials in patients with aHUS have shown that eculizumab is well tolerated and effective in both adult and paediatric patients with native or transplanted kidneys, whether or not a complement mutation has been identified [6, 7]. aHUS is a chronic disease, yet TMA manifestations are unpredictable and can lead to irreversible and potentially life-threatening complications. Therefore, life-long treatment with eculizumab is specified for patients with aHUS unless discontinuation is clinically indicated [8]. The dosing regimen in patients with aHUS was developed to maintain sufficient trough levels of eculizumab to sustain blockade of C5 between doses, including during potential periods of increased complement activation [7].

Despite our pathophysiologic understanding of aHUS and the label recommendation, reports of patients discontinuing eculizumab have been published. Among the justifications given are the wish to protect patients from potentially serious meningococcal infections, the risk of which is increased due to impaired complement-mediated lysis of *Neisseriae* [9, 10]. The prevention of other, rare, adverse events, such as immune-mediated drug reactions, and patient request have also been cited [11]. As with any life-long treatment, economic considerations exist and these have been discussed elsewhere [12]. Patients may also request to either continue or discontinue therapy and seek evidence to inform this decision.

This report will focus on available data for the medical evaluation of eculizumab discontinuation and TMA risk. Current evidence regarding discontinuation has been collated from case reports, clinical trials and the global aHUS Registry, and is discussed in light of the clinical experience of the authors.

Materials and methods

Patients with aHUS who discontinued eculizumab treatment were identified from three sources.

Identification of case studies of patients with aHUS who discontinued eculizumab

The authors analyzed their own cases of patients who had received eculizumab and subsequently discontinued treatment. In addition, a literature search was performed up to and including June 2015. The search used PubMed, and was limited to case reports or case series in English, using the terms 'atypical haemolytic uraemic syndrome' and 'eculizumab'. Both USA and UK spellings were used. Results were manually assessed for patient cases where treatment was discontinued after one or more doses of eculizumab.

Data from prospective and retrospective clinical trials including long-term follow-up studies

Patients who discontinued eculizumab while enrolled in any one of five eculizumab clinical trials, including long-term extensions, are reported [6, 7, 13, 14]. The safety and efficacy of eculizumab in patients with aHUS has been evaluated in four prospective, single-arm studies and one retrospective study. Study C08-003A/B, a prospective, open-label, single-arm study of 26 weeks (with a long-term extension), enrolled 20 adult and adolescent patients with long disease duration and chronic kidney injury undergoing prolonged plasma exchange/infusion at baseline [6]. Study C08-002A/B, a prospective, open-label, single-arm study of 26 weeks (with a long-term extension) in 17 adult and adolescent patients with clinical evidence of progressing TMA [6]. Two further prospective trials in adults (C10-004) and paediatric (C10-003) patients enrolled 41 and 22 patients with aHUS and signs of TMA, respectively [7, 14]. Study C09-001r was a retrospective, observational, non-interventional study of 30 adult/paediatric patients with aHUS treated with eculizumab [7]. In total, 130 patients with aHUS have enrolled in clinical studies. Patients who participated in any these studies are also eligible to enrol in a long-term follow-up (LTFU) study assessing the safety of eculizumab over up to 5 years.

The global aHUS Registry

The global aHUS Registry was initiated to record information on the natural history of patients with aHUS irrespective of treatment, prospectively collect safety and effectiveness data on patients treated with eculizumab, and provide LTFU on aHUS treatment with eculizumab. All patients clinically diagnosed with aHUS are eligible and data are collected at enrolment and every 6 months thereafter for a minimum of 5 years. The current analysis includes 296 patients receiving eculizumab enrolled in the Registry as of 29 August 2014 [15]. Further details on the global aHUS Registry methodology have recently been published [16].

Results

Authors' case reports

Unpublished cases of six patients from the authors' clinics are summarized in Table 1. Overall, eculizumab treatment duration ranged from 1 to 14 months. Following discontinuation, four patients had a subsequent TMA event between 2 and 12 months later and immediately restarted eculizumab treatment. Of these, two had no identified mutation, one had a C3 and the other a membrane cofactor protein (MCP) mutation. The clinical manifestation of TMA followed infection or vaccination in three of the four cases.

Published case reports

As of June 2015, case reports describing 52 patients who discontinued eculizumab after multiple doses, and 5 who received a

Table 1. Characteristics of six patients with aHUS discontinuing eculizumab treatment (unpublished author cases)

Case	Age (years)	Gender	Kidney status	Complement mutation	Time on eculizumab (months)	Reason for discontinuation	Time to new TMA event (months)	Reason for new TMA event	Treatment and/or outcome
1	39	M	Native	No mutation identified, homozygous CFH risk haplotype	1	Clinical improvement	–	–	Latest follow-up 19 months without overt TMA
2	16	F	Native	C3	6	Parent request	3	Upper airway infection	Long-term eculizumab
3	22	M	Native	No mutation identified	6	No recovery of renal function	2	Unknown	Long-term eculizumab
4	37	F	Native	MCP and homozygous CFH risk haplotype	4.5	Clinical improvement	3	Upper airway infection	Long-term eculizumab
5	37	F	DD KTx age 32 LD KTx age 37	MCP and homozygous CFH risk haplotype	3[a]	Considered stable	–	–	No overt TMA on reduced dose for 12 months
6	38	F	LD KTx age 30, second LD KTx age 38	No mutation identified	14	Patient request	12	Vaccination	Reinitiation of eculizumab
					6	Second patient request	4	Urinary tract infection	Long-term eculizumab

[a]In Case 5, patient did not discontinue but received a reduced dose of eculizumab (900 mg/month). CFH, complement factor H; DD, deceased donor; KTx, kidney transplant; LD, living donor; MCP, membrane cofactor protein; TMA, thrombotic microangiopathy.

single eculizumab dose were available [11, 17–39] (Table 2A and B, respectively). After discontinuation, within the limited follow-up reported, TMA manifestations were reported in 16 of 52 (31%) patients receiving multiple doses, and four of five (80%) receiving a single dose of eculizumab.

The reported reasons for discontinuation and subsequent causes of TMA following discontinuation are varied. Table 2A shows that three patients requested to stop treatment (two with an identified mutation and one not tested), one patient discontinued due to an infection and another due to progression to ESRD after eculizumab was initiated in late-stage disease. Infection led to TMA in both cases in which a cause was reported.

Most cases reporting a single eculizumab dose were reported in 2009 and 2010, prior to approval for the treatment of aHUS and before evidence from clinical trials of the safety and efficacy of long-term eculizumab treatment was widely available. Among these cases, the primary reason for discontinuation appears to be the substantial improvement in symptoms (Table 2B).

Ardissino *et al.* describe a case series of 22 patients with aHUS receiving eculizumab who were given the option to discontinue eculizumab after resolution of TMA symptoms [11]. Following explanation of the risk of new TMA manifestations, 12 patients decided to continue treatment [10 of whom had a complement factor H (CFH) mutation]. Ten patients discontinued eculizumab after a median treatment duration of 5.6 (range 0.4–14.2) months. A recent follow-up included a further six patients who had discontinued eculizumab [17]. Patients had no signs of active TMA at the time of discontinuation. Follow-up ranged from 0.4 to 40 months and 5/16 patients (31%) experienced new TMA manifestations. Eculizumab was reintroduced in all five patients, with renal function returning to pre-discontinuation levels [17]. One patient also restarted eculizumab pre-emptively prior to kidney transplant [11].

A review of the use of eculizumab in England included a description of 14 patients in whom eculizumab was withdrawn [34], in one case due to the diagnosis of typical HUS. Of the 13 patients with aHUS, three (23%) had evidence of recurrent TMA. Five patients were discontinued after ≥ 4 months of dialysis without apparent improvement in renal function, two of whom restarted eculizumab within 10 weeks due to significant haemolysis, which subsequently recovered. Of these, one patient carried a CFH/CFHR1 hybrid mutation; in the other, no mutation was identified. Of two patients with MCP mutations who discontinued eculizumab, one had a new TMA manifestation after 36 weeks leading to the reinitiation of eculizumab and recovery of renal function.

Dose modification has also been reported in three cases, two in which the dosing interval was extended and one in which the dose was reduced. Subsequent evidence of TMA was reported in all three patients, after intervals of 6 days, 10 days and 5 months, and included schistocytes, elevated lactate dehydrogenase or renal function deterioration [41–43]. After restarting eculizumab according to the approved dosing regimen, these parameters normalized.

Data from clinical trials and the global aHUS Registry

Initial and long-term outcomes from prospective studies have been reported elsewhere [6, 7, 13, 14]. Of interest here, 61 patients (including 21 paediatric patients) discontinued eculizumab treatment over the five clinical trials ($N = 130$), including extension studies and the LTFU. Selected demographics and

Table 2. Published case reports following discontinuation of eculizumab in 52 patients with aHUS (A) and patients with aHUS receiving a single eculizumab dose (B)

(A)

Case report	Kidney status	Mutation	Time on eculizumab	Reason for discontinuation[a]	Time to new TMA	Event underlying new TMA	Length of follow-up if no new TMA
Cayci *et al.* [19]	Native	CFI	3 weeks	Safety concern of long-term eculizumab	–	–	4 months
Garjau *et al.* [20]	Native	MCP	27 weeks	In ESRD, late eculizumab start	–	–	Not reported
Delmas *et al.* [23]	Native	CFH, CFI	Tapered after 18 months	Stable condition	–	–	2 months
Gulleroglu *et al.* [25]	Native	MCP	5 weeks	Normal neurological, renal, and haematological parameters	–	–	9 months
Canigral *et al.* [26]	Native	None identified	6 months	No mutation found	–	–	6 months
Fakhouri *et al.* [28]	Native	5 patients discontinued	3 weeks to 19 months	No detectable CFH antibodies, haemodialysis	–	–	5–13 months
De Sousa Amorim *et al.* [32]	Native	None identified, homozygous CFH and MCP risk haplotypes	11 months	Absence of TMA	–	–	12 months
Ardissino *et al.* [11, 17]	Native ($n = 10$) KTx ($n = 1$)	11/16 CFI, CFH antibodies, MCP, CFHR3/1 deletion	Median 4.3 (range 0.5–14.4) months	Physician-led patient decision	–	–	Range 0.4–40 months
Pu and Sido [30]	NR	None identified	12 weeks	Urinary infection	–	–	12 months
Sheerin *et al.* [34]	NR	11/14; none identified ($n = 6$), CFH, MCP, C3	1–34 weeks	No mutation identified ($n = 4$), still on dialysis at 4 months ($n = 3$), not aHUS ($n = 2$), MCP mutation ($n = 1$), non-compliance ($n = 1$)	–	–	Not reported, of patients with no identified mutations, 4 recovered, 2 are on dialysis, 2 patients died
Giordano *et al.* [21]	Native	CFH	18 months	Stable condition	45 days	No specific event reported (reduced platelet count and increased proteinuria)	–
Carr *et al.* [22]	Native	CFH	9 months	Patient request	6 months	Respiratory infection	–
Gilbert *et al.* [24]	Native	MCP	9 weeks	Cisplatin discontinuation and tumour excision	15 weeks	No specific event reported (elevated sC5b9 and renal biopsy results)	–
Ardissino *et al.* [11, 17]	Native	5/16 CFH, CFI, CFHR3/1 deletion, CFH antibodies	Median 4.3 (range 0.5–14.4) months	Physician-led patient decision	Range 0.7–17.3 months	Not reported	–

(continued)

Table 2. Continued

(A)

Case report	Kidney status	Mutation	Time on eculizumab	Reason for discontinuation[a]	Time to new TMA	Event underlying new TMA	Length of follow-up if no new TMA
Chaudhary *et al.* [27]	Native	Heterozygous for CFHR1-3, CFH point mutation	9 months	Patient request	Not reported	Pregnancy	
Kourouklaris *et al.* [29]	Native	Not tested	∼6 weeks	Patient request	5 months	No specific event reported (worsening anaemia, increased LDH and creatinine)	–
Schalk *et al.* [33]	Native	CFH	1 week (2 doses)	Assumed absence of effect	2 months	Not reported	–
Alachkar *et al.* [18]	LD KTx	None identified	8 months	Stable serum creatinine and normalization of laboratory and clinical parameters	5 months	Pneumonia	–
Wetzels *et al.* [31]	NR	3 patients CFH	4–6 months	Stable disease	3 months for one patient	Not reported	11–17 months for two patients
Sheerin *et al.* [34]	NR	3/14; none identified, CFH, MCP	24–27 weeks	Still on dialysis at 4 months ($n = 2$)	6–36 weeks	Haemolysis ($n = 2$)	–

(B)

Case report	Kidney status	Mutation	Reason for discontinuation[a]	Time to new TMA	Complement amplifying condition	Outcome
Mache *et al.* [35]	Native	No mutation identified	Improvement of renal function, platelet count normalization	2 weeks	Unknown	Eculizumab reintroduced, hypervolemic hypertension required haemodialysis, eculizumab discontinued again after the patient reached ESRD. A subsequent TMA complication resulted in anuria
Kose *et al.* (case 2) [37]	Native	CFH and CFI polymorphisms	Improvement of renal function, platelet count normalization	2 months	Unknown	Patient progressed to ESRD
Vilalta *et al.* [39]	Native	CFH	Normalization of renal function and haematological stabilization	8 weeks	Unknown	No new TMA events over subsequent 2.5 years eculizumab treatment
Nürnberger *et al.* [36]	DD KTx aged 30 and 37 years	CFH and CFHR1 deletion	Normalization of renal function and haemolysis markers	–	–	Stable renal graft function at 8 months (last reported follow-up)
Larrea *et al.* and Zuber *et al.* [38, 40]	DD KTx	CFH risk polymorphism	Single dose was planned	12 days	–	Eculizumab reintroduced

[a]As reported in published case study. aHUS, atypical haemolytic uraemic syndrome; CF, complement factor; CFHR, complement factor H receptor; DD, deceased donor; ESRD, end-stage renal disease; KTx, kidney transplant; LDH, lactate dehydrogenase; LD, living donor; MCP, membrane cofactor protein; NR, not reported; TMA, thrombotic microangiopathy.

Table 3. Demographics and disease characteristics at baseline and discontinuation for 61 patients discontinuing eculizumab in clinical trials

	Discontinuation with subsequent TMA event ($n = 12$)	Discontinuation without subsequent TMA event ($n = 49$)	All discontinued patients ($n = 61$)
Age at parent study baseline (years), median (range)	19.5 (0.0–80.0)	27.0 (0.0–68.0)	26.0 (0.0–80.0)
Female, *n* (%)	6 (50)	30 (61)	36 (59)
Identified complement mutation or autoantibody, *n* (%)	7 (58)	24 (49)	31 (51)
Factor H mutation	5 (42)	9 (18)	14 (23)
Time from TMA manifestation to start of eculizumab in parent trial (months), median (range)	0.7 (0.0–19.1)	0.8 (0.0–36.6)	0.8 (0.0–36.6)
Time from diagnosis to start of eculizumab in parent trial (months), median (range)	23.5 (0.0–112.5)	1.0 (0.0–288.0)	1.4 (0.0–288.0)
Duration of eculizumab treatment before discontinuation (weeks), median (range)	19 (1–116)	48 (1–231)	27 (1–231)
Time to TMA manifestation after discontinuation (weeks), median (min–max)	13 (4–127)	–	–
Follow-up time after discontinuation (weeks), median (min, max)	14 (4–151)	24 (0–145)	24 (0–151)
eGFR (mL/min/1.73 m^2), median (range)			
At parent study baseline	22.8 (10.0–105.5)	15.7 (5.3–102.0)	19.1 (5.3–105.5)
At discontinuation	36.5 (10.1–151.3)	42.9 (6.6–126.7)	41.5 (6.6–151.3)
Dialysis, *n* (%)			
At parent study baseline	4 (33)	20 (41)	24 (39)
At discontinuation	0 (0)	12 (25)	12 (20)
Kidney transplant before start of parent study, *n* (%)	3 (25)	13 (27)	16 (26)

eGFR, estimated glomerular filtration rate; TMA, thrombotic microangiopathy.

disease characteristics of these 61 patients are described in Table 3.

During a median follow-up period of 24 weeks after discontinuation, 12/61 patients (20%) experienced 15 severe TMA complications and 9 of these 12 patients restarted eculizumab (Table 4A). The median time to a TMA complication after discontinuation was 13 (range 4–127) weeks. Among patients who discontinued treatment, characteristics were similar between patients with and without TMA complications, except for a possibly higher proportion with a CFH mutation in the group experiencing TMA complications. None of the patients with new TMA events was on dialysis at the time of discontinuation. Following discontinuation, three patients with new TMA progressed to ESRD, one of whom required dialysis despite reinitiation of eculizumab. An additional two patients who received reduced eculizumab dosing experienced subsequent new TMA complications, resulting in ESRD in one patient (Table 4B).

Rates of eculizumab discontinuation and reinitiation have also been reported for 296 patients receiving eculizumab in the global aHUS Registry (data cut-off 29 August 2014). In patients aged <18 years, 28 (24%) discontinued, of whom 7 (25%) restarted eculizumab treatment. For adult patients, 48 (27%) discontinued and 5 (10%) subsequently restarted [15].

Discussion

Eculizumab, a first-in-class complement C5 inhibitor allowing specific blockade of terminal complement activation, is a well-tolerated and effective treatment for patients with aHUS. Moreover, the option of a pharmacologic intervention has drawn substantial scientific and clinical interest to the field, profoundly improving our understanding of the pathophysiology and clinical management of aHUS. Despite the understanding of a life-long inherent risk of unpredictable disease manifestations, which may be avoided by regulation of complement activation, patients may discontinue eculizumab therapy. The incidence, motivation and outcome of drug discontinuation are largely unknown or unreported. The present paper provides the most comprehensive review available to date, comprising not only the authors' personal experience and published cases, but also data from all clinical trials and the global aHUS Registry.

From the original clinical trials starting in 2008, 47% of patients had discontinued treatment by 2015. This includes patients who initiated eculizumab prior to availability of any trial data guidance on dosing and who in some cases only received a single dose; current evidence would not support the use of a single dose of eculizumab to treat aHUS. A more recent analysis of the aHUS Registry reveals a discontinuation rate of 26%. Among the trial population, 20% of patients experienced new TMA manifestations following discontinuation of eculizumab and organ losses were reported in 5% of cases (3/61 patients), in one case despite reinitiation of eculizumab. In the largest published case series [11, 17], 31% of patients who stopped eculizumab treatment experienced TMA manifestations after discontinuation. The variation reported here in TMA after eculizumab discontinuation likely represents differences in patient characteristics between those reported in case studies, treated in a clinical trial and enrolled in a patient registry.

When reported, the reasons for treatment discontinuation include both medical and economic concerns as well as patient request. These factors need to be weighed against the associated risk of treatment discontinuation. For adequate judgement, the availability of proper risk stratification and valid monitoring strategies are crucial. A number of factors potentially affecting associated risk of disease progression have been discussed, these include the underlying genetic disorder, age at first manifestation, previous TMA manifestations, prevalence of

Table 4. Patient characteristics and outcomes following discontinuation of eculizumab in clinical studies for 12 patients experiencing new TMA events (A) and following modification of eculizumab dosing (B) in clinical studies

(A)

Age at initial eculizumab treatment (years)	Kidney status	Mutation	Reason for discontinuation	Time to new TMA (weeks)	Restarted eculizumab?	Outcome
<1	Native	CFH	Did not enter extension	14	Yes	Not available
1	Native	CFH	Physician choice	8	Yes	Renal, haematological and cardiac improvement
4	Native	CFH	Did not enter extension	9	Yes	Not available
7	Native	CFI	Did not enter extension	77	Yes	Not available
15	Native	CFH	Did not enter extension	11	Yes	Renal and haematological improvement
18	Native	No mutation identified	Physician choice	4 (2 complications)	Yes	ESRD and haemodialysis
21	Native	MCP	Did not enter extension	84 and 153 (2 complications)	Yes	Not available
34	Native	CFH	Physician choice	14	Yes	Not available
29	Native	No mutation identified	Meningococcal meningitis	5	No	Progression to ESRD, haemodialysis
80	Native	No mutation identified	Lack of efficacy	127	No	Managed with PE and maintained elevated serum creatinine and low platelets
22	KTx	No mutation identified	Physician choice	<52 (2 complications)	Yes	Renal and haematological improvement
31	KTx	No mutation identified	Lack of renal improvement	4	No	ESRD

(B)

Age at initial treatment (years)	Kidney status	Mutation	Modification of dosing[a]	Restarted standard eculizumab dosing regimen?	Outcome
30	KTx	C3	1200 mg: Every 3 weeks for 6 weeks Single doses after a further 6, 13 and 17 weeks	No	Sepsis, renal impairment, gastrointestinal bleeding and other complications leading to death due to multi-organ failure
43	KTx	CFI	1200 mg: Once a month for 1 month Every 2 weeks for 8 weeks Once a week for 5 weeks (due to adverse event of renal impairment) Every 2 weeks for 12 weeks Every 3 weeks for 3 weeks	No	Progressed to ESRD, haemodialysis initiated and eculizumab discontinued

[a]Recommended dosing for adult patients with atypical haemolytic uraemic syndrome is 900 mg weekly for the first 4 weeks, followed by 1200 mg for the fifth dose 1 week later, then 1200 mg every 2 weeks thereafter. CF, complement factor; ESRD, end-stage renal disease; KTx, kidney transplant; MCP, membrane cofactor protein; PE, plasma exchange; TMA, thrombotic microangiopathy.

extrarenal manifestations, post-transplant setting and pregnancy-associated disease.

Some reports suggest a potential relationship between the type of complement mutation identified and the risk of subsequent clinical manifestations of TMA. Patients with CFH mutations appear to be at higher risk [11], although the exon in which the mutation is located may play a pivotal role [31]. It has also previously been demonstrated that patients with CFH or thrombomodulin mutations had the earliest onset of aHUS and the highest mortality, whereas MCP mutations were associated with the least severe outcomes [4]. However, it has been reported that patients without identified mutations have similarly poor outcomes to patients with identified mutations, thereby suggesting that the risk of new TMA manifestations in these groups is comparable [44]. Also, we report three patients with MCP mutations (Tables 1 and 2) who experienced a new TMA event following eculizumab discontinuation, indicating the risk in such patients.

TMA manifestations have been described in patients of all ages. A previous TMA manifestation may identify patients with

a high susceptibility to complement-activating conditions, and current clinical understanding would advocate not to discontinue treatment of a patient who has already had a life-threatening TMA manifestation. Children represent a high-risk group, in that common events leading to complement activation (i.e. infections or vaccinations) are frequent in this age group. Recent paediatric guidelines state that withdrawal should not be considered in children with life-threatening symptoms upon presentation or those not fully having recovered renal function [45].

The risk of TMA manifestation increases in some conditions, such as organ transplantation. In contrast to aHUS patients with native kidneys, a post-transplant setting incurs a number of additional potential TMA risk factors, including the allograft endothelium, immunosuppressants and related infections. Also, with the reduced nephron mass of a single transplanted kidney, recovery from a TMA manifestation is more modest than in patients with native kidneys [46–48]. Another example is pregnancy, with the risk of a TMA manifestation in aHUS increasing dramatically after parturition and loss of local complement regulation [49]. Despite often being stated, avoiding further pregnancy does not limit the risk of further clinical TMA manifestation. This is illustrated by Case 6, which reports pregnancy-associated aHUS manifesting again after transplantation in response to common complement-amplifying conditions (Table 1).

Current evidence suggests that new TMA risk following discontinuation is unpredictable [50]. Since defective complement regulation in aHUS results in continuous overactivation of the alternative complement pathway [4, 51, 52], reliable biomarkers of overall complement activity and disease progression are essential. A simple haemolytic assay with patient serum and sheep erythrocytes has been described for assessing complement activation. However, this assay only appeared sensitive in patients with CFH-related aHUS [53, 54], and only measures complement activation in serum and not at the endothelial cell surface. Measurement of complement proteins in plasma is of limited value: in patients with genetic mutations in CFH, MCP, CFI and thrombomodulin or with anti-CFH antibodies, reduced C3 levels have been found in only 30–50% of cases [4]. A recent study demonstrated the proportion of patients with increased levels of C5a and sC5b9 in plasma were similar during subclinical disease (58% and 64% of patients, respectively) and active disease (47% and 53% of patients, respectively) [55]. In contrast, the same study found that C5b9 deposits from patients' sera on an *in vitro* cultured human cell line showed good correlation to disease activity [55]. Despite measuring complement activity at the site of injury (i.e. the endothelial level), and for the first time showing a correlation to clinical disease activity, this cell-based assay is limited by availability and is not routinely clinically applicable. Currently, functional tests of complement activity and measurement of complement proteins does not provide unequivocal data allowing the presence or indeed absence of aHUS to be confirmed. Therefore, the optimum strategy for monitoring complement activation and the evolution of aHUS—particularly in identifying ongoing subclinical TMA, which may not manifest with clinical symptoms—is not clear and remains a key question for the future.

When TMA occurs after discontinuation, restarting eculizumab and subsequent long-term use can prevent further TMA manifestations. Vilalta *et al*. report TMA manifesting 8 weeks after a single eculizumab dose; the patient then remained TMA event-free over a further 2.5 years of ongoing eculizumab treatment [39]. However, in one patient from a clinical trial, and the case of Mache *et al*. [35], the restart of eculizumab could not prevent deterioration of renal function, TMA and subsequent ESRD. Aside from renal recovery, there are patients who benefit from resolution of debilitating extrarenal TMA manifestations such as cardiovascular or central nervous system involvement [1, 51]. An example is Case 3 (Table 1), who despite continued dependence on dialysis remained free from acute presentation and gastrointestinal symptoms on long-term eculizumab treatment.

Discontinuing eculizumab therapy potentially puts patients at risk in two ways: firstly, the risk of progressive disease and new TMA and, secondly, the risk of not experiencing the reported clinical benefits of long-term therapy. A feature of the prospective trials was the improvement in renal function over a period of >2 years (C08-002A/B, C08-003A/B) [13], and therefore, for many patients, continuous therapy may result in ongoing benefit.

In summary, on the basis of current evidence and clinical understanding, discontinuation of eculizumab may increase the risk of further clinical manifestations of TMA, which are unpredictable in severity and timing. It is not yet clear whether patients with or without identified genetic mutations are at higher risk of new TMA manifestations when eculizumab is discontinued. The current data are limited due to being based on published clinical cases and retrospective analysis of clinical trial data, as well as being constrained by the limited duration of follow-up reported. Observational studies such as the aHUS Registry and the aHUS LTFU study will be a key source of data for future analyses of outcomes for patients with aHUS. Additional efforts are underway to collect more clinical evidence through the EVIDENCE study (NCT02614898). The purpose of this study is to assess TMA manifestations in patients with aHUS whether or not treated with eculizumab. Until tools are available to provide more robust risk stratification and adequately monitor complement activation and disease activity, the option to discontinue eculizumab will not be an evidence-based decision. More comprehensive collection of data on discontinuation and its consequences will empower informed decision making by clinicians and patients.

Conflict of interest statement

N.H. and F.d.A.M. have received consulting fees from Alexion Pharma GmBH. N.H., F.d.A.M., T.D., I.F., K.H. and M.M. received travel expenses and honoraria from Alexion Pharma GmBH for attending an advisory board. C.G. is an employee and stakeholder of Alexion Pharma GmBH.

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