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ORIGINAL ARTICLE

Eculizumab interruption in atypical hemolytic uremic syndrome due to shortage: analysis of a Brazilian cohort

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Abstract

Background The risk of eculizumab therapy discontinuation in patients with atypical hemolytic uremic syndrome (aHUS) is unclear. The main objective of this study was to analyze the risk of aHUS relapse after eculizumab interruption due to drug shortage in Brazil.

Methods We screened all the registered dialysis centers in Brazil (n = 800), willing to participate in the aHUS Brazilian shortage cohort, through electronic mail and formal invitation by the Brazilian Society of Nephrology. We included patients with aHUS whose eculizumab therapy underwent unplanned discontinuation for at least 30 days between January 1st, 2016 and December 31st, 2019 during the maintenance phase of treatment. Relapse was defined by the development of thrombocytopenia, hemolytic anemia, acute kidney injury or thrombotic microangiopathy (TMA) in a kidney biopsy.

Results We analyzed 25 episodes of exposure to risk of relapse, from 24 patients. Median age was 33 (6–53) years, 18 (72%) were female, 9 (36%) had a functioning renal graft, 5 (20%) were undergoing dialysis. *CFH* variant was found in 8 (32%) episodes. There were 11 relapses. The risk of relapse was 34%, 44.5% and 58% at 114, 150 and 397 days, respectively. No baseline variable was related to relapse in Cox multivariate analysis, including *CFH* variant.

Conclusions In this study, the cumulative incidence of aHUS relapse at 397 days was 58% after eculizumab interruption. The presence of complement variant does not seem to be associated with a higher relapse rate. The eculizumab interruption was deemed not safe, considering that the rate of relapse was high.

Keywords Atypical hemolytic uremic syndrome · Eculizumab · Complement inactivating agents

Introduction

Atypical hemolytic uremic syndrome (aHUS) is complement-mediated thrombotic microangiopathy (TMA) caused by dysregulated activity of the alternative pathway. aHUS is an ultra-rare disease with a reported incidence of approximately 0.5 per million per year. At least half of the patients have an inherited and/or acquired complement abnormality [1].

After approval of eculizumab, a humanized monoclonal antibody against C5, by the *US Food and Drug Administration* and the *European Medicines Agency* in 2011, prospective studies have shown safety and efficacy of terminal complement-inhibition in the management of adults and children with aHUS [2–5].

(Although eculizumab is a life-long treatment, its high cost and risk of severe adverse effects, such as meningococcal infection, have been under discussion with the discontinuation of eculizumab therapy [6–8].)

Some retrospective studies assessed the discontinuation of eculizumab therapy in aHUS patients but there are still no conclusive results. Pathogenic variants in complement genes

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have been associated with a higher rate of aHUS relapse [8–11]. Prospective studies are being performed to investigate the safety of discontinuation under a planned protocol (NCT 02574403).

In Brazil the medication is provided by the government under judicial decision and aHUS patients receive the drug through federal purchases. In 2017, the Brazilian federal police conducted an operation to investigate fraud in purchases of drugs that are used to treat rare diseases, including eculizumab [12]. After that, the National Press reported many cases of eculizumab interruption due to a shortage in Brazil. This tragic episode provided an opportunity for a natural experiment to evaluate the course of unplanned eculizumab discontinuation and episodes of aHUS relapses.

Materials and methods

Study population

Through electronic mail and formal invitation by the Brazilian Society of Nephrology, we screened all dialysis centers in Brazil (n = 800) that were interested in taking part in the aHUS Brazilian shortage cohort.

Inclusion and exclusion criteria

We included patients with aHUS who discontinued eculizumab therapy for at least 30 days, between January 1st, 2016 and December 31st, 2019 in the maintenance phase of eculizumab (more than 6 months of eculizumab use). The discontinuation of eculizumab was unplanned and motivated by the government supply shortage.

We excluded patients with planned discontinuation or discontinuation for medical reasons. Patients with a doubtful diagnosis of aHUS or only non-complement-related genetic variants (Diacylglycerol Kinase Epsilon—*DGKE*) were also excluded. DGKE-mediated aHUS was excluded as it is eculizumab non-responsive [13].

Renal transplant patients did not necessarily receive a diagnosis of aHUS prior to kidney transplantation.

Therapy

All the patients had undergone approved intravenous eculizumab dose (900 mg/week for 4 weeks, 1,200 mg at week 5 and then every 2 weeks indefinitely).

We defined interruption as at least 30 days without receiving a maintenance dosage of the eculizumab (lack of at least 2 doses of the drug), without a patient and medical decision based on genetic investigation.

Definition of aHUS

The diagnosis of aHUS was established by the finding of thrombotic microangiopathy, defined by the triad: microangiopathic hemolytic anemia (decreased hemoglobin, presence of fragmented red blood cells, increased LDH, negative direct Coombs test), thrombocytopenia or 25% decrease in the number of platelets and decreasing glomerular filtration rate, exclusion of the use of drugs, infections or other potential secondary causes [14]. Thrombotic thrombocytopenic purpura and Shiga toxin-producing *E. coli*-associated hemolytic uremic syndrome were excluded in all cases. The diagnoses, which were made by primary care physicians, were reviewed when the cases were elected to the Brazilian cohort study.

Clinical data

Evaluated data were age, sex, time on eculizumab therapy, kidney status (native kidney, kidney transplant with functioning renal graft, undergoing dialysis), and genetic study.

Genetic analysis

For the atypical hemolytic uremic syndrome panel, the entire coding region of the *ADAMTS13, C3, CD46, CFB, CFH, CFHR1, CFHR2, CFHR3, CFHR5, CFI, DGKE, PIGA, THBD* genes including 10 bp of intronic flanking sequences were amplified and sequenced in the majority of cases. In Brazil, all analyses are performed according to the protocol described by Lilian et al. [15]. Antibody anti-CFH level was not performed because it is unavailable in Brazil.

We divided variants according to loss of function (*CFH, CFHR1, CFHR1-CFHR3, CFHR5, CFI*), gain of function (*C3*) and non-complement-related genetic variants (*DKGE*). All identified variants were evaluated regarding their pathogenicity and causality. All variants except benign or likely benign variants were reported.

Exposure to risk

The exposure to the risk of aHUS relapse was assessed when a patient under regular eculizumab treatment (more than 100 days) discontinued the use of the drug for more than 30 days (2 doses). If the patients resumed the use of eculizumab for more than 6 months and then had therapy interrupted again, we considered that as a new episode risk.

Primary endpoint

We considered aHUS relapse as the primary endpoint. Relapse was defined as the presence of at least two of the following features, (ruled out an alternative diagnosis):

1. Thrombocytopenia (platelet count $< 150 \times 10^3/\mu L$).
2. Mechanical hemolytic anemia (Hb < 10 g/dL, LDH > upper limit of normal, undetectable haptoglobin, presence of fragmented red blood cells on blood smear).
3. Acute kidney injury (> 1.5 × serum creatinine increase from baseline).
4. Features of thrombotic microangiopathy (glomerular and/or arteriolar thrombi, double contours of glomerular basement membrane, detachment of endothelial cells) in performed kidney biopsy at the time of suspected relapse.

Outcomes

Hemolytic anemia investigation was performed by using blood count associated with platelet count and fragmented red blood cells, LDH and haptoglobin measurement. Analysis of kidney function was performed by measuring serum creatinine. Urinalysis results were not provided. These clinical variables were evaluated before and after eculizumab interruption. We also evaluated the clinical outcomes of death and need to start dialysis.

Relapses were treated by the primary care physicians according to local protocols of treatment—including plasmapheresis—because eculizumab was unavailable at that time. The only child who received the drug—with remission—for a few months was an exception.

Statistical analysis

Baseline variables are presented as mean and standard deviation and median and interquartile ranges when appropriate. We used the Kaplan–Meier survival analysis to estimate the risk of relapse over time. A Cox regression model was used to evaluate predictors that might be associated with relapse (primary endpoint). The analysis was done in R 3.6.3 with the survival and survminer package.

Results

Baseline characteristics

We retrieved data from 11 different centers throughout Brazil out of 800 centers. We screened 25 patients with aHUS and 26 episodes of exposure to risk after interruption of eculizumab therapy. One patient was excluded (only *DKGE* variant). We analyzed 24 patients with 25 episodes of exposure to risk (Fig. 1). Median age was 33 (6–53) years, 18 (72%) were female, 9 (36%) had a functioning renal graft and 5 (20%) were undergoing dialysis. In 22 episodes, eculizumab use had been ongoing for longer than 365 days before interruption (Table 1). The majority of discontinuation episodes occurred in 2017 (n = 21, 84%).

Genetic characteristics

Among all episodes, 16 (64%) were associated with any complement variant. *CFH* variant was found in 8 (32%) episodes, *CFHR1-CFHR3* variant in 8 (32%) and *C3* variant in 5 (20%) (Table 1).

Relapses

We had a total of 11 cases of relapses in the 25 episodes that were evaluated. The risk of aHUS relapse was 34% at 114 days, 44.5% at 150 days and reached the maximum of 58% at 397 days (Fig. 2). One transplant patient lost their graft and restarted hemodialysis, whilst another patient died, both cases were associated with aHUS relapse (Fig. 3). In our sample, no extra-renal manifestations were reported.

We assessed the relapses in patients with *CFH* variant. No differences were found in patients with or without the *CFH* variant in the Kaplan–Meier cumulative incidence analysis (Fig. 4).

We ran a Kaplan–Meier analysis of patients with and without functioning kidney graft (supplementary 1). Although the renal transplant patients seemed to relapse earlier, we found no statistical difference between these two groups (p = 0.31).

In the Cox regression multivariate analysis, we assessed age, sex, dialysis, kidney transplant, and genetic characteristics as independent predictors of relapse after eculizumab

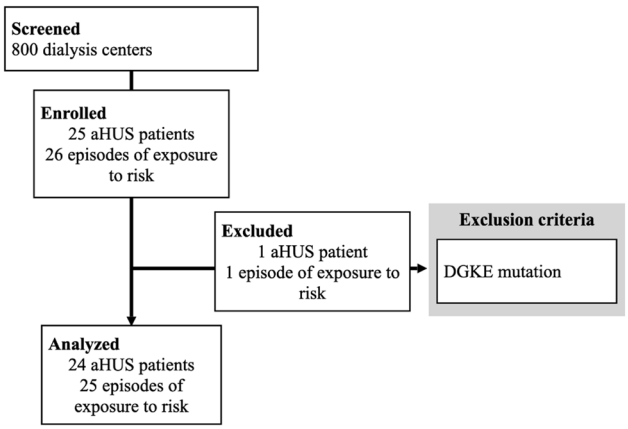

Fig. 1 Study flow diagram

Table 1 Baseline characteristics according to episodes of exposure to risk after eculizumab therapy discontinuation

Parameters	n = 25
Median age, years (range)	33 (6–53)
Sex, n (%)	
Female	18 (72)
Male	7 (28)
Kidney transplant, n (%)	9 (36)
Dialysis, n (%)	5 (20)
Duration of drug use (days), n (%)	
< 365	3 (12)
150	1 (4)
182	1 (4)
350	1 (4)
> 365	22 (88)
Complement genes, n (%)	
Any variant identified	16 (64)
CFH	8 (32)
CFI	2 (8)
C3	5 (20)
CFHR1-CFHR3	8 (32)
CFHR1	2 (8)
CFHR5	4 (16)
CFB	1 (4)
None	4 (16)
Not investigated	5 (20)

No genetic variant was identified by a aHUS panel

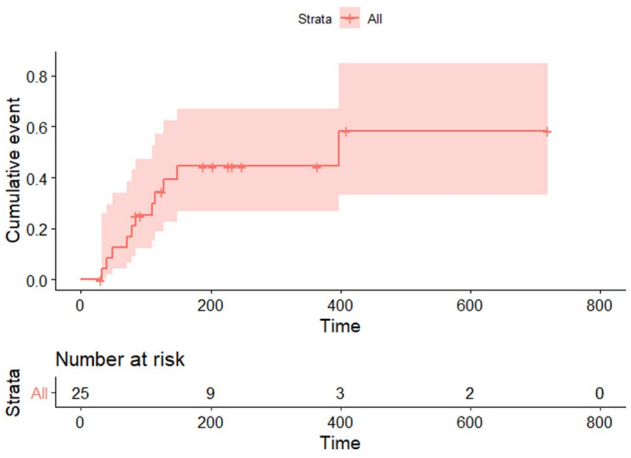

Fig. 2 One minus cumulative incidence of aHUS relapse

discontinuation. None of these variables were associated with aHUS relapse (Table 2). All the episodes of exposure to risk and their clinical characteristics, standardized genetic findings [16], and the presence of aHUS relapse are reported in Table 3.

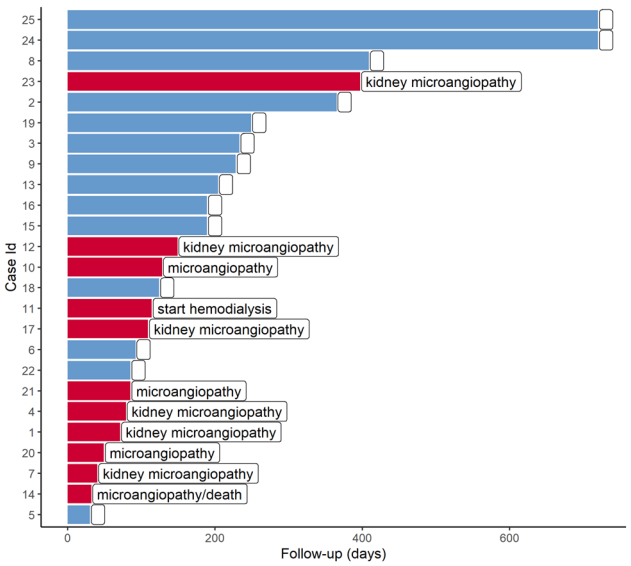

Fig. 3 Outcomes over time in each episode of exposure to risk. Microangiopathy = laboratory features of hemolytic anemia or thrombocytopenia; Kidney microangiopathy = kidney injury and laboratory features of hemolytic anemia or thrombocytopenia

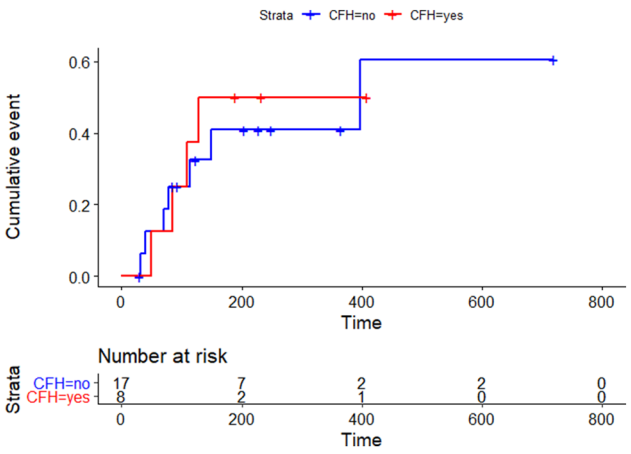

Fig. 4 Comparative incidence of relapsing in patients with or without CFH

Discussion

In this study we evaluated 25 episodes of eculizumab interruption in 24 patients with aHUS and found a high rate of aHUS relapse. Due to the lack of clinical trials the possibility of eculizumab discontinuation remains unclear. Other published observational studies analyzed eculizumab discontinuation and showed an incidence of aHUS relapse of about 30% [10, 11, 15], whereas the present study showed a higher incidence in an unplanned discontinuation (58%).

The majority of eculizumab interruption episodes occurred in 2017 and were probably due to legal issues

Table 2 Independent predictors of relapsing after eculizumab discontinuation in multivariate Cox regression analysis

Variables	Cox regression analysis	
	HR (95% CI)	p value
Age	0.97 (0.89–1.04)	0.38
Sex, male	0.84 (0.15–4.7)	0.84
Dialysis	0.50 (0.03–7.28)	0.61
Kidney transplant	1.37 (0.25–7.65)	0.72
Variant: none	1.49 (0.18–12.13)	0.71
Variant: not investigated	0.68 (0.05–8.52)	0.77
Variant: *CFH*	1.23 (0.23–6.64)	0.81

Age is per year; sex male yes or no; patient in dialysis yes or no; functioning kidney transplant yes or no; variant: none, not investigated; *CFH* yes or no. HR, hazard ratio; 95% CI, 95% confidence interval

related to drug availability, leading to difficulties in supply. Impossibility to acquire the medication led most of the physicians to adopt a close monitoring approach without a specific protocol. The patients did not have immediate access to the medication to treat aHUS relapse. Besides a higher rate of aHUS relapse, two major events occurred in this cohort causing death and loss of kidney graft.

(In our cohort were identified any type of genetic variants in 64% of the episodes. Most part of them were *CFH*, *C3*, and *CFI*.) The *CFH* variant, which is a frequent variant in aHUS cases, was shown to be related to the earliest onset and high risk of relapse in some Italian and French studies. Our multivariate analysis did not show a higher incidence of relapse among episodes of exposure to risk related to the *CFH* variant, although the relatively small sample size may explain these findings. In addition, our cohort has very specific genetic characteristics, such as the absence of the *CD46* variant and the impossibility to detect antibodies against factor H. However, we did find a higher prevalence of the *C3* variant than in the Italian and French cohorts [9–11, 17].

Eculizumab deposits in renal arterioles can remain detectable until 5 months after drug withdrawal [18]. Therefore, a residual inhibitory effect on the complement system could justify the late appearance of relapses.

We had 44% of relapses in 9 episodes of risk in patients with functioning renal graft. Recurrent TMA may depend on genetic abnormalities in renal transplantation [19]. Furthermore, clinical manifestations and histopathological features may not be present at the same time [1]. Perhaps protocol biopsy after eculizumab discontinuation should be performed to identify relapses during the follow-up of these aHUS patients.

The discontinuation studies used laboratory and clinical features related to TMA as a diagnostic tool to assess relapse in aHUS patients [8–11]. The decision to resume the drug before the occurrence of unfavorable outcomes—clinical manifestations or overt TMA—must lay on a detailed follow-up of both eculizumab levels and complement activity. Future perspectives might move towards restrictive use and individualized prescription [20].

This study is retrospective and presents limitations. Several collaborators collected data from medical records. All exams, including genetic studies, were performed in different laboratory centers. This study screened a small number of patients with an ultra-rare disease and perhaps the follow-up time was not long enough to assess outcomes, especially in milder variants. Not all dialysis centers participated—only 11 out of 800 in Brazil—in the analysis, and thus possibly more patients at risk were not included in the study. In addition, we included patients undergoing dialysis (who provide limited features about)??? renal results. Despite these limitations, this study had an unfortunate but unique opportunity to evaluate abrupt eculizumab interruption.

In conclusion, the cumulative incidence of aHUS relapse reached 58% after 397 days of eculizumab discontinuation. The eculizumab interruption was deemed not safe, considering that the rate of relapse was high. In this cohort, despite the study limitations described above, the presence of *CFH,* the complement variant, does not seem to be associated with a higher rate of relapse. Very important implications in ethical and financial terms require eculizumab interruption to be avoided.

Table 3 Characteristics of patients who had their eculizumab therapy discontinued

Episodes	Sex	Age (years)	Kidney status	Duration of therapy (days)	Duration of discontinuation (days)	Relapse	Genes	Genetic description[b]	Allele frequency GnomAD/ABraOM
1	F	38	Tx	> 365	71	Yes	Not investigated		
2	M	34	Tx	> 365	365	No	None		
3	M	25	Tx	> 365	233	No	*CFH* *CFHR1-CFHR3*	Heterozygous variant *CFH* (c.3148A>T; p.Asn1050Tyr) Homozygous deletion in *CFH* Homozygous deletion encompassing in *CFHR1-CFHR3* Homozygous likely pathogenic deletion ecompassing exon 23 in *CFH*	1.47e−2/1.64e−2 – – –
4	F	37	Tx	> 365	79	Yes	None		
5	M	33	Tx	350	30	No	*C3* *DGKE*	Heterozygous variant *C3* (c.463A>C; p.Lys155Gln) Heterozygous VUS in *DGKE* (c.318C>G; p.Phe106Leu)	2.7e−3/ND 1.87e−4/ND
6	F	19	Tx	> 365	92	No	None		
7	M	34	Tx	150	40	Yes	*CFI CFB*	Heterozygous likely PV in *CFI* (c.1246A>C; p.Ile416Leu+c.1071T>G; p.Ile357Met) Heterozygous VUS in *CFB* (c.1505T>C; p.Ile502Thr)	1.22e−3/4.1e−3 3.58e−5/8.2e−4 2.03e−5/ND
8	F	25	Native	> 365	409	No	*CFH* *CFHR5*	Heterozygous variant *CFH* (c.1111C>A; p.His371Asn) Heterozygous variants *CFHR5* (c.232T>C; p.Ser78Pro+c.835T>A; p.Tyr279Asn+c.986_988del; p.Lys329del)	8.15e−5/ND 1.2e−4/ND + 1.27e−4/ND + 7.83e−5/ND
9	M	46	Native	> 365	228	No	Not investigated		
10	F	43	Dialysis	> 365	128	Yes	*CFH* *C3*	Heterozygous PV in *CFH* (c.3473C>G; p.Ser1158*) Heterozygous VUS in *C3* (c.3593A>G; p.Gln1198Arg)	ND/ND 3.98e−5/ND
11	F	27	Tx	182	114	Yes	*C3* *CFI* *CFHR1-CFHR3*	Heterozygous variant *C3* (c.193A>C+p.Lys65Gln) Heterozygous variant *CFI* (c.530A>T+p.Asn177Ile) Heterozygous deletion ecompassing in *CFHR1-CFHR3*	4.77e−5/8.2e−4 6.37e−5/8.2e−4 –
12	F	21	Native	> 365	149	Yes	*CFHR1-CFHR3*	Heterozygous VUS deletion in *CFHR1-CFHR3*	–
13	F	33	Native	> 365	204	No	*C3* *CFHR1 CFHR1-CFHR3*	Heterozygous variant *C3* (c.3100T>C; p.Trp1034Arg) Homozygous variant *CFHR1* (c.614C>T; p.Thr205Met) Heterozygous VUS deletion in *CFHR1-CFHR3*	ND/ND 5.81e−2/ND -
14	F	30	Native	> 365	32	Yes	none		
15	F	46	Dialysis	> 365	189	No	*CFH*	Homozygous likely PV in *CFH* (c.1756C>T; p.Gln586*)	ND/ND
16	F	53	Dialysis	> 365	189	No	*CFH*	Homozygous likely PV in *CFH* (c.1756C>T; p.Gln586*)	ND/ND
17	F	34	Native	> 365	109	Yes	*CFH*	Heterozygous variant *CFH* (c.3572C>T; p.Ser1191Leu)	ND/ND
18	F	32	Native	> 365	124	No	Not investigated		
19	F	34	Dialysis	> 365	249	No	Not investigated		
20[a]	M	6	Native	> 365	49	Yes	*CFH* *CFHR1-CFHR3* *CFHR5*	Heterozygous PV in *CFH* (c.3548G>T; p.Trp1183Leu) Heterozygous deletion encompassing in *CFHR1-CFHR3* Heterozygous VUS in *CFHR5* (c.1664G>C; p.Arg555Pro)	ND/ND – 8.13e−5/1.64e−3
21[a]	M	6	Native	> 365	85	Yes	*CFH* *CFHR1-CFHR3* *CFHR5*	Heterozygous PV in *CFH* (c.3548G>T; p.Trp1183Leu) Heterozygous deletion encompassing in *CFHR1-CFHR3* Heterozygous VUS in *CFHR5* (c.1664G>C; p.Arg555Pro)	ND/ND – 8.13e−5/1.64e−3
22	F	36	Tx	> 365	85	No	*CFHR1* *CFHR5*	Heterozygous VUS involving duplication *CFHR1* in exon 6 Heterozygous VUS in *CFHR5* (c.254-2_266dup; p.Ser88_Phe89insLeuGlyMetCysSer)	– 9.26e−4/ND

Table 3 (continued)

Episodes	Sex	Age (years)	Kidney status	Duration of therapy (days)	Duration of discontinuation (days)	Relapse	Genes	Genetic description[b]	Allele frequency GnomAD/ABraOM
23	F	29	Native	> 365	397	Yes	*C3* *CFHR1-CFHR3*	Heterozygous VUS in *C3* (c.188C>G; p.Pro63Arg) Homozygous VUS deletion in CFHR1-CFHR3	ND/ND –
24	F	30	Native	> 365	720	No	*CFHR1-CFHR3*	Heterozygous deletion in *CFHR1-CFHR3*	–
25	F	31	Dialysis	> 365	720	No	not investigated		

Tx transplant (functioning renal graft); *none* not identified mutation after genetic study; *PV* pathogenic variant; *VUS* variant of unknown significance; *CFH* complement factor H; *CFHR1*, *CFHR3*, *CFHR5* CFH-related genes CFHR1, CFHR3, CFHR5; *CFI* complement factor I; *CFB* complement factor B, *DGKE* diacylglycerol kinase epsilon

GnomAD: Genome Aggregation Database (https://gnomad.broadinstitute.org)

ABraOM: Brazilian Genomic Variants (http://abraom.ib.usp.br)

[a]Different episodes of the same patient

[b]Pathogenic variants was described according to American College of Medical Genetics and Genomics (ACMG)

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Author contributions MEN and LGMA were involved in the conception and design of the research, and interpreted the results. MEN was the main author and LGMA provided mentorship and performed statistical analysis. MEN, LGMA, LMS, HVGV, HSN, AMB, JCAB, RCG, RBVK, RMQ, VBBMS, APN, MIH, LMPP, MHV and GMK contributed to collecting data and revising the article. All authors edited, revised and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest M.I.H., M.H.V., L.M.P.P. and L.G.M.A. have received fees for participation in teaching courses from Alexion Pharmaceuticals as speakers. M.E.N., L.M.S., H.V.G.V, H.S.N., A.M.B., J.C.A.B., R.C.G., R.B.V.K., R.M.Q., V.B.B.M.S., A.P.N. and G.M.K. have no competing interests to declare.

Ethical approval The study protocol was approved by the Ethics Committee of Universidade Estadual Paulista (UNESP), São Paulo State University (ethics number: 2.772.340). The study was performed according to the Declaration of Helsinki. All participants provided written consent.

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