

Eculizumab Safety: 5-Year Experience from the Global aHUS Registry

SUPPLEMENTARY MATERIAL

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Table S1. Deaths in adult ever-treated patients

Cause of death	Patient age ^a (years)	Eculizumab treatment at time of SAE/death	Additional details
aHUS	22	Yes	<ul style="list-style-type: none"> • Patient received 1 dose of eculizumab subsequent to TMA manifestation and was reported to have acute respiratory failure, which was assessed as serious and severe, the next day • Patient died on the same day due to acute heart failure
Cancer	45	No	<ul style="list-style-type: none"> • Patient with history of cervical cancer received <1 month of treatment with eculizumab • One year after eculizumab discontinuation, the patient had respiratory distress and died due to cervical cancer
Cancer	50	Yes	<ul style="list-style-type: none"> • Patient had history of acute myeloid leukemia and

			thrombophlebitis
			<ul style="list-style-type: none"> • After 2 years of eculizumab treatment, the patient died due to acute myeloid leukemia and acute aspergillosis
Cancer	55	Yes	<ul style="list-style-type: none"> • Patient with transplanted kidney received eculizumab treatment for several years • Patient developed glioblastoma and died a month later while receiving eculizumab
Cancer	55	No	<ul style="list-style-type: none"> • Patient with history of pancreatic cancer received eculizumab for 1 year • Patient discontinued eculizumab, reported acute myeloid leukemia, and died 1 month later
Cancer	67	No	<ul style="list-style-type: none"> • Patient with medical history of pancreatic cancer and hypertension received eculizumab for 1 month • Three years later, the patient died due to renal failure, aHUS, and stage IV pancreatic cancer

Cancer	70	No	<ul style="list-style-type: none">• Patient previously received 2 months of eculizumab treatment and discontinued, with requirement for chronic dialysis and history of hepatic impairment• Two years later, the patient was hospitalized with a medically significant AE of liver disorder and had a 9-month history of malignant neoplasm• Patient died due to hepatic impairment with encephalopathy (hepatocellular carcinoma and ethylic cirrhosis)
Cardiovascular event	22	Yes	<ul style="list-style-type: none">• Patient with history of hypertension and multiple events of thrombosis• Five months after initiation of eculizumab, the patient was reported to have hyperglycemia and died 1 month later due to cardiac arrest

Cardiovascular event	33	No	<ul style="list-style-type: none">• Patient with aHUS triggered by pregnancy and requiring chronic dialysis received 2 doses of eculizumab postpartum• Two years after eculizumab discontinuation, the patient died due to acute cardiorespiratory failure
Cardiovascular event	36	No	<ul style="list-style-type: none">• Patient initiated eculizumab at time of renal transplant and discontinued after 3 years• Three months later the patient was hospitalized for cerebral hemorrhage and hypertension, having started dialysis again 2 months prior• Patient died due to cerebral bleeding
Cardiovascular event	70	No	<ul style="list-style-type: none">• Patient with history of malignancy and renal impairment received eculizumab for 1 month and then started chronic dialysis 5 months post-discontinuation of eculizumab• Patient died 3 years later due to an acute myocardial

			infarction
Gastrointestinal event	41	Yes	<ul style="list-style-type: none"> • Patient with transplanted kidney and long history of aHUS • Eculizumab was initiated after a TMA manifestation and 2 months later the TMA was still ongoing • One month later, 2 separate events of gastrointestinal hemorrhage were reported • Patient discontinued eculizumab, experienced the second gastrointestinal event, and then died 2 days later due to continuous gastrointestinal bleeding
Infection	22	Yes	<ul style="list-style-type: none"> • Patient was treated with eculizumab for 8 months and then fulminant meningococemia was reported • Patient died on the same day
Infection	24	No	<ul style="list-style-type: none"> • Patient, with history of renal impairment, transplant, and hypertension, underwent a second renal transplant combined with liver transplant

- Patient received 3 total doses of eculizumab beginning at the time of the second transplant and discontinued 1 week later
- One month following the transplant, the patient was hospitalized twice due to recurrent bacterial and *Aspergillus* infections
- Patient died 3 months post-transplant due to a ruptured cerebral aneurysm related to the *Aspergillus* infection

Infection

27

Yes

- Patient, with history of systemic lupus erythematosus, died 1 year after initiation of eculizumab treatment due to sepsis

Infection

40

Yes

- Patient with history of hypertension was hospitalized for a serious infection 10 months after starting eculizumab
- Patient died 1 month later due to respiratory failure and pneumonia while hospitalized

Infection

55

No

- Patient with history of renal impairment and hypertension

was given 2 doses of eculizumab, but dialysis could not be discontinued

- Patient was hospitalized for infection 6 months after discontinuing eculizumab
- At the same instance, AEs of coronary artery disease, seizure, and renal impairment were reported; pneumonia developed 2 months later
- Ten months after discontinuing eculizumab, the patient was hospitalized for renal impairment and died; the cause of death was reported as sepsis and multiple organ failure

Infection

55

No

- Patient with transplanted kidney required chronic dialysis, despite receipt of eculizumab treatment for 6 months
 - Patient was hospitalized 5 times due to single episodes of infection (3 while on eculizumab and 2 after discontinuation)
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- The last infection was reported as bacteroid bacteremia 4 months after discontinuation of eculizumab and 2 weeks before death
 - The cause of death was reported as unknown

Infection 74 Yes

- Patient with history of renal and hepatic impairment was hospitalized for a serious infection 2.5 months after start of eculizumab
- Patient discontinued eculizumab and died 11 days later due to the serious infection leading to multiple organ failure while hospitalized

Infection 77 No

- Patient on chronic dialysis received treatment with eculizumab for 1 month
 - Patient was hospitalized for sepsis, 10 months after discontinuing eculizumab, with ongoing TMA; the patient died 2 days later due to sepsis
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Unknown	19	Yes	<ul style="list-style-type: none">• Patient was on chronic dialysis with medical history of hypertension, pneumonia, and renal impairment• Patient had been on eculizumab treatment for 1 year when reported to have died (“sudden death”)
Unknown	37	Yes	<ul style="list-style-type: none">• Patient received treatment with eculizumab 8 months and then was reported to have died by sudden death
Unknown	65	Yes	<ul style="list-style-type: none">• Patient with history of hypertension, renal impairment, and ductal carcinoma was on chronic dialysis• After 2 months of ongoing eculizumab, events of encephalopathy began to occur• Six-seven months later hypertensive encephalopathy, gastrointestinal hemorrhage, and ischemic stroke were reported while the patient was still on eculizumab• Patient was discovered dead at home 2 months later and the cause of death was reported as unknown

Unknown	66	No	<ul style="list-style-type: none"> • Patient with a long medical history of systemic lupus erythematosus, arthritis, renal impairment, and infections was on chronic dialysis • Patient had been treated for 3 months with eculizumab, and died 7 months post-discontinuation due to unknown cause
Unknown	80	No	<ul style="list-style-type: none"> • Patient with medical history of malignant hypertension was treated for 2 months with eculizumab • Patient died 2 weeks after last dose of eculizumab and the cause of death is unknown

^aPatient age at enrollment in the Registry.

AE, adverse event; aHUS, atypical hemolytic uremic syndrome; SAE, serious adverse event; TMA, thrombotic microangiopathy.

Table S2. Deaths in adult never-treated patients

Cause of death	Patient age^a (years)	Additional information
aHUS	23	<ul style="list-style-type: none">• Patient was reported with cardiac failure, which was assessed as serious and severe, and died due to cardiomyopathy on the same day
aHUS	62	<ul style="list-style-type: none">• Patient experienced renal impairment, which was assessed as serious and severe, and was attributed to aHUS• Patient died the same day due to multiorgan failure
aHUS	65	<ul style="list-style-type: none">• Patient died due to TMA complication
aHUS	74	<ul style="list-style-type: none">• Patient died due to renal impairment
aHUS	81	<ul style="list-style-type: none">• Patient was hospitalized for renal impairment and was also reported to have acute kidney injury and cardiac failure; all 3 events were assessed as serious and severe

		<ul style="list-style-type: none"> • Renal impairment was attributed to coexisting disease • Patient died <1 week later due to acute renal failure and heart failure
aHUS	83	<ul style="list-style-type: none"> • Patient was reported with renal impairment, which was assessed as serious and severe, and was attributed to coexisting disease • Patient died on the same day due to renal impairment
Cancer	49	<ul style="list-style-type: none"> • Patient died due to breast carcinoma
Cancer	66	<ul style="list-style-type: none"> • Patient died ≈2 months following enrollment due to terminal anal cancer
Cancer	68	<ul style="list-style-type: none"> • Patient was hospitalized for malignant neoplasm, which was assessed as serious and severe, and was attributed to coexisting disease • Patient died 2 days later due to liver metastases
Cancer	74	<ul style="list-style-type: none"> • Patient was reported with end-stage renal disease, which was assessed as serious and severe • Patient died on the same day due to prostate cancer and withdrawal from dialysis

Cancer	78	<ul style="list-style-type: none">• A single episode of malignant neoplasm was reported, which was assessed as serious and severe, and was attributed to coexisting disease• Patient died <2 months later due to leukemia
Cardiovascular event	51	<ul style="list-style-type: none">• Patient died due to respiratory and cardiovascular failure
Cardiovascular event	55	<ul style="list-style-type: none">• Patient was reported with supraventricular tachycardia, which was assessed as serious and moderate, and was then reported with 2 device-related infections, which were assessed as serious and moderate, 1 to 2 months later• After ≈1 month, the patient was then reported with right ventricular failure, which was assessed as serious and severe• Patient died 1 week later due to right heart failure after pulmonary infarction
Cardiovascular event	63	<ul style="list-style-type: none">• Patient was reported with aortic dissection, which was assessed as serious and severe; the event was considered resolved in <1 month

		<ul style="list-style-type: none"> • After ≈8 months, the patient was hospitalized for cardiac failure, which was assessed as serious and severe • Patient died <2 weeks later due to heart failure
Cardiovascular event	72	<ul style="list-style-type: none"> • Patient was hospitalized for renal impairment and was also reported to have arrhythmia; both of these events were assessed as serious and severe • Patient died the same day due to malignant cardiac arrhythmias
Cardiovascular event	86	<ul style="list-style-type: none"> • Patient was hospitalized for tricuspid valve incompetence, which was assessed as serious, severe, and was attributed to the underlying study indication • Patient died <3 weeks later due to severe tricuspid valve failure
Drug-related event	57	<ul style="list-style-type: none"> • Patient died due to respiratory failure secondary to bleomycin lung injury while hospitalized
Gastrointestinal event	47	<ul style="list-style-type: none"> • Patient was hospitalized for a liver disorder, which was assessed as serious and severe, and was attributed to the underlying study

		<p>indication</p> <ul style="list-style-type: none"> • Patient died the next day due to hepatic impairment
Gastrointestinal event	59	<ul style="list-style-type: none"> • Patient died due to an intestinal perforation, which was assessed as serious and severe
Infection	22	<ul style="list-style-type: none"> • Patient was hospitalized for cytomegalovirus infection, which was assessed as serious and severe and was attributed to coexisting disease, and died the next day from respiratory arrest probably due to cytomegalovirus
Infection	23	<ul style="list-style-type: none"> • Patient was hospitalized for 3 events of infection, which were assessed as serious and severe, and were attributed to an “other” cause • Patient died from bacteremia due to enterococcal infection
Infection	24	<ul style="list-style-type: none"> • Patient was hospitalized for a single episode of infection, which was assessed as serious and severe and attributed to coexisting disease immediately following enrollment • The event was considered resolved in <1 month

		<ul style="list-style-type: none"> • Patient subsequently died 3 weeks later due to acute respiratory failure
Infection	61	<ul style="list-style-type: none"> • Patient was hospitalized for continuous infection, which was assessed as serious and severe, and was attributed to coexisting disease • Patient died <1 month later due to bronchopneumonia and chronic obstructive pulmonary disease
Infection	62	<ul style="list-style-type: none"> • Patient was hospitalized for sepsis, which was assessed as serious and severe, and was attributed to coexisting disease • Patient died 1 day later due to sepsis
Infection	63	<ul style="list-style-type: none"> • Patient died due to sepsis
Infection	75	<ul style="list-style-type: none"> • Patient was hospitalized for sepsis, which was assessed as serious and severe, and was attributed to the coexisting disease • Patient died due to protracted cardiogenic shock and pulseless ventricular tachycardia while hospitalized on the same day
Other	54	<ul style="list-style-type: none"> • Patient was hospitalized for a medically significant adverse event of spinal cord compression, which was assessed as serious and severe,

and was attributed to an “other” cause

- Patient died 4 days later due to acute respiratory failure

^aPatient age at enrollment in the Registry.

aHUS, atypical hemolytic uremic syndrome; TMA, thrombotic microangiopathy.