Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Clinical Research Letter

Canadian Journal of Kidney Health and Disease
Volume 8: 1–5

DOI: 10.1177/20543581211003763
journals.sagepub.com/home/cjk
SAGE

Prophylactic or Early Use of Eculizumab and Graft Survival in Kidney Transplant Recipients With Atypical Hemolytic Uremic Syndrome in the United States: Research Letter

Richard A. Plasse[1,2], Stephen W. Olson[1,2], Christina M. Yuan[1,2], Lawrence Y. Agodoa[3], Kevin C. Abbott[4], and Robert Nee[1,2]

Abstract

Introduction: Among kidney transplant recipients (KTRs) with end-stage kidney disease (ESKD) due to atypical hemolytic uremic syndrome (aHUS), recurrence is associated with poor allograft outcomes. We compared graft and patient survival of aHUS KTRs with and without prophylactic/early use of eculizumab, a monoclonal antibody that binds complement protein C5, at the time of transplantation.

Methods: We conducted a retrospective cohort study using the United States Renal Data System. Out of 123 624 ESKD patients transplanted between January 1, 2008, and June 1, 2016, we identified 348 (0.28%) patients who had "hemolytic uremic syndrome" as the primary cause of ESKD. We then linked these patients to datasets containing the Healthcare Common Procedure Coding System (HCPCS) code for eculizumab infusion. Patients who received eculizumab prior to or within 30 days of transplant represented the exposure group. We calculated crude incidence rates and conducted exact logistic regression, adjusted for recipient age and sex, for the study outcomes of graft loss, death-censored graft loss, and mortality. We also estimated the average treatment effect (ATE) by propensity-score matching, to reduce the bias in the estimated treatment effect on graft loss.

Results: Our final study cohort included 335 aHUS KTRs (23 received eculizumab, 312 did not), with a mean duration of follow-up of 5.8 $\pm$ 2.7 years. There were no significant differences in baseline demographic and clinical characteristics between the eculizumab versus non-eculizumab group. Patients who received prophylactic/early eculizumab were less likely to experience graft loss compared with those who did not receive eculizumab (0% vs 20%, $P = .02$), with an adjusted odds ratio of 0.13 ($P = .02$). In the propensity-score-matched sample, the ATE (eculizumab vs non-eculizumab) was −0.20 (95% confidence interval [CI] = −0.25 to −0.15, $P < .001$); thus, treatment was associated with an average of 20% reduction in graft loss. There was no significant difference in the risk of death between the 2 groups.

Conclusions: Although there was no significant difference in the risk of death, prophylactic/early use of eculizumab was significantly associated with improved graft survival among aHUS KTRs. Given the high cost of eculizumab, randomized controlled trials are much needed to guide prophylactic strategies to prevent graft loss.

Abrégé

Introduction: Chez les receveurs d'une greffe rénale (RGR) dont l'insuffisance rénale terminale (IRT) est due au syndrome hémolytique et urémique atypique (SHUa), la récidive est associée à de mauvais résultats d'allogreffe. Nous avons comparé la survie du greffon et des patients RGR-SHUa avec et sans administration prophylactique/précoce d'éculizumab, un anticorps monoclonal qui lie la protéine C5 du complément, au moment de la transplantation.

Méthodologie: Nous avons mené une étude de cohorte rétrospective en utilisant le *United States Renal Data System*. Parmi les 123 624 patients atteints d'IRT transplantés entre le 1er janvier 2008 et le 1er juin 2016, nous avons répertorié 348 (0,28 %) patients présentant un «syndrome hémolytique urémique» comme cause principale de l'IRT. Nous avons ensuite lié ces patients à des ensembles de données contenant le code du *Healthcare Common Procedure Coding System* (HCPCS) pour la perfusion d'éculizumab. Les patients ayant reçu de l'éculizumab avant l'intervention ou dans les 30 jours suivant la transplantation représentaient le groupe d'exposition. Nous avons calculé les taux bruts d'incidence et procédé à une régression logistique exacte, corrigée selon l'âge et le sexe du receveur, pour les résultats de l'étude concernant la perte du

greffon, la perte du greffon censurée par le décès et la mortalité. Nous avons également estimé l'effet de traitement moyen (ETM) par appariement des scores de propension, afin de réduire le biais de l'effet estimé du traitement sur la perte du greffon.

Résultats: Notre cohorte d'étude finale comprenait 335 patients RGR-SHUa (23 ayant reçu de l'éculizumab et 312 n'en ayant pas reçu) dont le suivi s'établissait à 5,8 ± 2,7 ans. Aucune différence significative n'a été observée entre les caractéristiques cliniques et démographiques initiales des deux groupes de sujets. Les patients ayant reçu de l'éculizumab prophylactique/précoce étaient moins susceptibles de subir une perte du greffon que ceux qui n'en avaient pas reçu (0 % vs 20 %; $P = 0{,}02$), avec un rapport de cotes corrigé de 0,13 ($P = 0{,}02$). Dans l'échantillon aux scores de propension appariés, l'ETM (éculizumab vs sans éculizumab) était de −0,20 (IC 95 %: −0,25 à −0,15; $P < 0{,}001$), le traitement a donc été associé à une réduction moyenne de 20 % de la perte du greffon. Aucune différence significative n'a été observée entre les deux groupes quant au risque de décès.

Conclusion: Bien qu'aucune différence significative n'ait été observée pour le risque de mortalité, l'administration prophylactique/précoce d'éculizumab a été associée de façon significative à une amélioration de la survie du greffon chez les patients RGR-SHUa. Étant donné le coût élevé de l'éculizumab, des essais contrôlés randomisés sont nécessaires pour orienter les stratégies prophylactiques visant à prévenir la perte du greffon.

Keywords

atypical HUS, eculizumab, kidney transplantation, thrombotic microangiopathy, alternative complement pathway, renal graft survival, death-censored graft survival, mortality, end-stage kidney disease, USRDS, HCPCS

Received January 21, 2021. Accepted for publication February 12, 2021.

Introduction

Atypical hemolytic uremic syndrome (aHUS), a thrombotic microangiopathy due to complement dysregulation from genetic or autoimmune disinhibition of the alternate complement pathway, can cause end-stage kidney disease (ESKD). The introduction of eculizumab, a C5-targeted complement inhibitor, has significantly improved overall disease prognosis and renal survival.[1] Recurrence of aHUS after kidney transplantation, as determined by complement genetic abnormalities, is associated with an increased risk of graft loss and death.[2,3] However, data on the impact of prophylactic eculizumab on graft survival in kidney transplant recipients (KTRs) with ESKD due to aHUS have been obtained mainly from enrolled patients in aHUS registries.[4,5] Using the United States Renal Data System (USRDS), a well-established national-level database, we compared graft and patient survival of aHUS KTRs with and without prophylactic/early eculizumab at the time of transplantation.

Methods

We conducted a retrospective cohort study using the USRDS, which incorporates baseline and follow-up demographic and clinical data on nearly all patients accessing the Medicare ESKD program in the United States. We identified 123 624 ESKD patients who were transplanted between January 1, 2008, and June 1, 2016, of whom 348 (0.28%) had "hemolytic uremic syndrome" (HUS) as the primary cause of ESKD (Centers for Medicare and Medicaid Services [CMS] Medical Evidence Form 2728 diagnosis codes: 28311, 2831A, D593). Although the diagnosis codes do not differentiate between typical and atypical HUS, the majority of these patients likely had the latter condition because it is much more likely to lead to ESKD compared with those with typical HUS (eg, Shiga toxin-producing *Escherichia coli* [STEC]).[6] We then linked these aHUS KTRs to datasets containing Healthcare Common Procedure Coding System (HCPCS) code for eculizumab infusion (Code J1300, "Injection, eculizumab, 10 mg"). The earliest date of eculizumab use in the dataset was on April 20, 2011, which aligned with the U.S. Food and Drug Administration (FDA) approval of its treatment indication for aHUS in 2011.

The exposure group was defined as those patients who received eculizumab prior to or within 30 days of transplant, because initiation of therapy after 30 days is unlikely to represent a prophylactic indication. Therefore, our primary analyses excluded patients who were initiated on eculizumab

[1]Nephrology Service, Walter Reed National Military Medical Center, Bethesda, MD, USA
[2]Department of Medicine, Uniformed Services University, Bethesda, MD, USA
[3]Office of the Director, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA
[4]Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

Corresponding Author:
Robert Nee, Nephrology Service, Walter Reed National Military Medical Center, 8901 Wisconsin Avenue, Bethesda, MD 20889, USA.
Email: robert.nee.civ@mail.mil

Table 1. Risk of Graft Loss and Death, Eculizumab Versus No Eculizumab.

	Percentages[a]			Crude incidence rates (per 1000 patient-years)			Adjusted odds ratio[b] (eculizumab vs no eculizumab)		
Exposure group	Overall graft loss	Death-censored graft loss	Death	Overall graft loss	Death-censored graft loss	Death	Overall graft loss	Death-censored graft loss	Death
Eculizumab (n = 23)	0 (0%)	0 (0%)	0 (0%)	0	0	0	0.13 (95% CI = 0-0.74)	0.18 (95% CI = 0-1.05)	0.38 (95% CI = 0-2.38)
No eculizumab (n = 312)	64 (20.5%)	48 (15.4%)	26 (8.3%)	35 (95% CI = 27-45)	26 (95% CI = 20-35)	13 (95% CI = 9-20)			
P value	.02	.04	.15	.02	.04	.13	.02	.06	.35

Note. CI = confidence interval.
[a]Data are n (%).
[b]Adjusted for recipient age and sex.

after 30 days post-transplant (n = 8) and after development of graft loss (n = 5). Our final study cohort consisted of 335 aHUS KTRs (23 received prophylactic/early eculizumab, 312 did not receive any eculizumab). Discontinuance of therapy was defined as those patients whose last infusions were greater than 30 days before the last date of HCPCS dataset (December 30, 2016). We did not restrict age in our study cohort. The primary outcome was overall graft loss (including death with graft function), and the secondary outcomes were death-censored graft loss and mortality.

Patients and Sources

The files SAF.PATIENTS were used as the primary dataset and SAF.MEDEVID for additional information coded in the Medical Evidence Form 2728. The HCPCS data were obtained from Institutional REV claim files 2008-2012 and DET claim files 2013-2016 (Revenue Center Details Standard Analysis Files).

Statistical Analysis

Analyses were performed using Stata MP/16.1 (Stata Corp, College Station, Texas). Univariate analyses were performed with chi-square testing for categorical variables, Student *t* test for continuous variables, and nonparametric tests (Mann-Whitney) for non-normal distributions. We calculated percentages and crude incidence rates of overall graft loss, death-censored graft loss, and mortality. The follow-up period for incidence rate calculation for graft loss was censored at death or end of study (August 1, 2018). We conducted exact logistic regression analyses which provide more reliable statistical inference with small samples than standard logistic regression. The primary predictor variable in the regression model was prophylactic/early eculizumab use, adjusted for recipient age and sex. Furthermore, we estimated the average treatment effect (ATE) by propensity-score matching. Specifically, we used a logistic regression model to estimate propensity scores, incorporating the following confounding variables: recipient age, sex, presence of acute rejection, use of calcineurin inhibitor, and donor type (living vs deceased). After nearest neighbor matching 1:1 by propensity score, we computed the ATE of the matched sample.

Results

Our cohort consisted of 335 aHUS KTRs (23 received eculizumab, 312 did not), with a mean duration of follow-up of 5.8 ± 2.7 years. The majority of these patients were female, white, and less than 30 years old (Supplemental Table). There were no significant differences in baseline demographic and clinical characteristics between the eculizumab versus non-eculizumab group.

Twenty-three out of 335 (7%) aHUS KTRs received prophylactic/early eculizumab. The median number of infusions per patient was 42 (interquartile range [IQR] = 16, 66). Treatment was initiated at a median of -7 days (IQR = −138, 22) from transplant, with a median duration of therapy of 798 days (IQR = 379, 1103). The median payment amount per patient was US$706 518 (IQR = US$241 237, US$1 306 453).

Eculizumab was discontinued in 9 out of 23 patients (39%), after a median prophylactic duration of 329 days (IQR = 127, 791). The median number of infusions was 24 (IQR = 6, 37) prior to discontinuation of eculizumab. Mean duration of follow-up for these 9 patients was 5.6 ± 1.8 years.

As shown in Table 1, patients who received prophylactic/early eculizumab were less likely to experience graft loss compared with those who did not receive eculizumab (0% vs 20%, $P = .02$). Death-censored graft loss for the eculizumab versus non-eculizumab cohort was 0% versus 15%, respectively ($P = .04$). The adjusted odds ratios (eculizumab vs non-eculizumab) of graft loss and death-censored graft loss were 0.13 ($P = .02$) and 0.18 ($P = .06$), respectively. In the propensity-score-matched sample, the ATE (eculizumab vs non-eculizumab) was −0.20 (95%

confidence interval [CI] = −0.25 to −0.15, $P < .001$); thus, treatment was associated with an average of 20% reduction in graft loss. There was no significant difference in the risk of death between the 2 groups.

Discussion

We report the first examination of eculizumab therapy in the aHUS KTR population in the United States, using national-level data. Conducting both adjusted logistic regression and propensity-score models, we found that prophylactic/early eculizumab use was significantly associated with lower risk of graft loss, which is consistent with prior observational studies based on aHUS registry data.[4,5] Indeed, none of the treated patients developed graft loss. Our findings also revealed potentially underutilization and heterogeneity in the use of eculizumab in the United States, that is, 7% versus 41% of kidney transplants from the French aHUS registry.[5] This could be related to differences in cohort characteristics based on identified genetic abnormalities[7] and risk for aHUS recurrence, variation in clinical practice, and cost barriers. With a median cost of US$706 518 per patient in our study, careful consideration of this therapy is warranted.[8] For instance, findings from a small case series suggested that living kidney donor transplantation in aHUS without prophylactic eculizumab was achievable using a protocol that emphasized lower target calcineurin inhibitor level, strict blood pressure control, and use of renin-angiotensin-aldosterone system blockade and statins.[9]

None of the 9 patients who discontinued eculizumab experienced graft loss, after receiving a median of 24 infusions. Since standard maintenance regimens are every other week, our data suggest that discontinuation of eculizumab is feasible after 1 year. Although genetic profiles are important in assessing the risk of aHUS recurrence after treatment cessation,[10] information on eculizumab withdrawal after transplantation remains very scarce.[5] Thus, our findings help to close the knowledge gap in the duration of prophylaxis in aHUS KTRs.

Our study has certain limitations. First, the USRDS is largely an administrative database and does not provide detailed clinical information. Although the majority of the study cohort likely had aHUS as the primary cause of ESKD, it is possible that a smaller subset of these patients had typical HUS (STEC). Furthermore, the clinical phenotype and genotype of the study cohort that can inform the risk of recurrence after transplantation were unknown, the underlying etiology of graft loss was unknown, and data on therapeutic plasma exchange were not available. Second, the eculizumab group may have included patients who were treated for aHUS recurrence many months before transplantation (while on dialysis) as well as those who may have been treated for aHUS recurrence in the early post-transplant period. Third, given the possibility of confounding by indication to the extent that the decision to use eculizumab may be dependent on the patients' baseline clinical characteristics, we conducted propensity-score modeling to reduce the bias in the estimated treatment effect. Fourth, we cannot make conclusions about causality given the retrospective nature of this study. Last, the sample size is relatively small, reflecting the rarity of aHUS. Nonetheless, our findings reflect real-world clinical practice and a broad representation of the racially and ethnically diverse ESKD population in the United States.

Conclusions

Although there was no significant difference in the risk of death, prophylactic/early use of eculizumab was significantly associated with improved graft survival among aHUS KTRs. Our study adds to the mounting compelling evidence of benefit with prophylactic/early use eculizumab in the peritransplant setting. Given the retrospective design of the study, however, our results should be considered hypothesis generating and serve to instruct potential prophylactic strategies to prevent graft loss in future randomized controlled trials.

Ethics Approval and Consent to Participate

The protocol (353086-18) was approved by the Walter Reed National Military Medical Center (WRNMMC) Department of Research Programs as exempt from IRB review, not involving human subjects.

Consent for Publication

Consent for publication was obtained from all authors.

Availability of Data and Materials

We are unable to make available our dataset in accordance with the guidelines of the USRDS Agreement for Release of Data (Data Use Agreement). Researchers can request Standard Analysis Files (SAFs) from the USRDS (https://www.usrds.org/for-researchers/standard-analysis-files/).

Disclaimer

The views expressed in this Research Letter are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, the Department of Defense, National Institutes of Health, or the United States Government.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Robert Nee https://orcid.org/0000-0003-1201-6344

Supplemental Material

Supplemental material for this article is available online.

References

1. Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) controversies conference. *Kidney Int*. 2017;91(3):539-551.
2. Tanriover B, Lakhia R, Shen YM, et al. Characteristics and outcomes of renal transplant recipients with hemolytic uremic syndrome in the United States. *Transplant Direct*. 2015;1(10):e41.
3. Le Quintrec M, Zuber J, Moulin B, et al. Complement genes strongly predict recurrence and graft outcome in adult renal transplant recipients with atypical hemolytic and uremic syndrome. *Am J Transplant*. 2013;13(3):663-675.
4. Siedlecki AM, Isbel N, Vande Walle J, James Eggleston J, Cohen DJ, Global aHUS Registry. Eculizumab use for kidney transplantation in patients with a diagnosis of atypical hemolytic uremic syndrome. *Kidney Int Rep*. 2018;4(3):434-446.
5. Zuber J, Frimat M, Caillard S, et al. Use of highly individualized complement blockade has revolutionized clinical outcomes after kidney transplantation and renal epidemiology of atypical hemolytic uremic syndrome. *J Am Soc Nephrol*. 2019;30(12):2449-2463.
6. Fakhouri F, Zuber J, Frémeaux-Bacchi V, Loirat C. Haemolytic uraemic syndrome. *Lancet*. 2017;390(10095):681-696.
7. Fremeaux-Bacchi V, Fakhouri F, Garnier A, et al. Genetics and outcome of atypical hemolytic uremic syndrome: a nationwide French series comparing children and adults. *Clin J Am Soc Nephrol*. 2013;8(4):554-562.
8. van den Brand JA, Verhave JC, Adang EM, Wetzels JF. Cost-effectiveness of eculizumab treatment after kidney transplantation in patients with atypical haemolytic uraemic syndrome. *Nephrol Dial Transplant*. 2017;32(suppl 1):i115-i122.
9. Duineveld C, Verhave JC, Berger SP, van de Kar NCAJ, Wetzels JFM. Living donor kidney transplantation in atypical hemolytic uremic syndrome: a case series. *Am J Kidney Dis*. 2017;70(6):770-777.
10. 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(1):50-59.