KI REPORTS
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Every Fifteen Days Forever?

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Kidney Int Rep (2023) **8,** 4–7; https://doi.org/10.1016/j.ekir.2022.11.006

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Atypical hemolytic uremic syndrome (aHUS) is a rare but usually severe form of thrombotic microangiopathy that manifests clinically with microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.[1]

Rare variants in genes that encode the complement regulators, factor H, factor I, membrane-cofactor protein, and thrombomodulin or the 2 components of the alternative pathway C3 convertase, C3, and factor B, as well as anti-FH antibodies have been found in 50% to 60% of patients with aHUS.[2]

For decades, plasma exchange or infusion has been the sole therapeutic option for patients with aHUS, but the response has been variable. Mortality during the acute episode was up to 20%, and over 50% of surviving patients developed end-stage kidney disease within 3 years of diagnosis.[2,3] These outcomes were dictated by the underlying complement gene abnormality. Mortality and the development of end-stage kidney disease were highest among patients with factor H or C3 mutations and lowest in those with membrane-cofactor protein mutations.[2,3]

More than 20 years of research have highlighted the important role that uncontrolled activation of the complement alternative pathway plays in this devastating disease, but the outcome for these unfortunate patients suddenly changed in 2012 with the approval of eculizumab, a monoclonal humanized antibody that binds to C5 and prevents the formation of C5a and the C5b-9 membrane attack complex, as a specific treatment for aHUS.[4] Indeed, eculizumab has radically transformed the natural history of aHUS. Clinical trials and common practice have shown that the most aHUS patients respond to C5 inhibition, and the risk of end-stage kidney disease in treated patients has decreased to 10% to 15%.[4,5]

The optimal duration of eculizumab treatment has not yet been determined, and life-long therapy is recommended in current regulatory guidance, because of concerns about the risk of aHUS relapses and further kidney injury. However, the risk of potentially fatal meningococcal infections, the need for repeated intravenous infusions, and the extremely high cost of the drug have provided the urgent need to find ways to discontinue treatment after achieving stable clinical remission.[6]

Case reports and series, as well as retrospective studies, have shown that eculizumab withdrawal may be feasible, but have also highlighted the risk of relapses, particularly in patients with complement gene variants.[6] A recent systematic review of the literature that includes 280 aHUS patients from 40 publications reports a 29.6% relapse rate after therapy discontinuation.[6] Decreasing age, the presence of a renal allograft, and the detection of rare variants in factor H, membrane-cofactor protein, or C3 genes were all independently associated with relapse.

A further step forward was taken by 2 prospective studies.[7,8] The larger study,[8] includes 55 patients who were in stable remission while they were treated with eculizumab for at least 6 months, and then discontinued the drug. During the 2-year follow-up, 23% of patients experienced a relapse. In multivariable analysis, the presence of a rare gene variant was associated with an increased risk of relapse, which led to the conclusion that a discontinuation strategy based on complement genetics could be reasonable and safe.[8] Importantly, among the 13 patients who relapsed, all of whom restarted eculizumab, 11 regained their baseline renal function and only 1 progressed to end-stage kidney disease, suggesting that close monitoring and immediately restarting eculizumab might allow discontinuation in at-risk patients as well.[8]

In this issue of *KI Reports*, Bouwmeester *et al.*[9] describe the results of a new prospective study, CUREiHUS, which monitored eculizumab discontinuation in Dutch pediatric and adult patients with aHUS in the native kidneys who received first time eculizumab

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treatment and experienced full hematological recovery and renal response after starting therapy. During the follow-up after eculizumab discontinuation, 1 or more relapses occurred in 4 patients; all of them during the first year, always preceded by viral-like infections. Eculizumab was reinitiated within 24 hours of the clinical manifestations of relapses and resulted in the normalization of hematological parameters and recovery of renal function following all events. At last follow-up, patients who had relapsed experienced no chronic sequelae. The authors conclude that eculizumab discontinuation in well-defined and closely monitored aHUS patients is feasible and safe.[9]

This study strengthens our confidence about discontinuing eculizumab in aHUS patients who are in stable remission. What it contributes to the literature is an extensive evaluation and the use of very strict criteria for patient recruitment, which excluded patients with secondary forms of thrombotic microangiopathy, with suspected aHUS in a transplanted kidney, and patients who remained on dialysis after eculizumab. The finding that over 70% of patients had complement genetic variants plays in favor of inclusion of very well characterized patients. Another merit of this study is the unbiased design, because all recruited patients underwent eculizumab discontinuation even though for some this was preceded by a tapering period. The study also provides an extensive cost-consequence analysis that includes all medical costs in addition to eculizumab. The analysis shows that eculizumab withdrawal reduced the medical costs per patient by 70%, without negatively affecting quality of life.[9]

Unfortunately, the CUREiHUS study lacks the power to identify clinically relevant predictors of relapse because of the low sample size ($n = 18$ patients were included in the analysis), and event rate (4 relapsing patients for a total of 9 relapses). The limitation particularly applies to the evaluation of the predictive role of complement gene variants. In line with previous published studies, all 4 patients who relapsed after the discontinuation of eculizumab, carried at least 1 complement pathogenic variant. However, only 2 patients in the cohort did not carry genetic abnormalities. With a 22% relapse rate, the likelihood of a relapse occurring in this subgroup was too low to draw any conclusions. The fact that after eculizumab discontinuation 1 of the 2 patients without complement gene variants had an episode of thrombotic microangiopathy, which however resolved spontaneously, further removes any possibility of confirming or disproving the hypothesis that the absence of a complement gene variant is a negative predictor of relapses.

additional limitation of the CUREiHUS study,[9] is the wide range of follow-up times after eculizumab discontinuation (between 0 and 237 weeks), so that the risk exposure time differed greatly between patients. In a few patients, the follow-up was much shorter than the median time of relapse occurrence in this cohort (19.5 weeks), and it is not possible to tell whether they will or will not have a relapse later on.

Regardless of the above considerations, the new study, along with the previously published retrospective and prospective studies, [6–9,S1-S4] show that even in the high-risk group of aHUS patients with pathogenic or likely pathogenic complement gene variants, 50% to 75% of patients will not relapse.

Should we offer high-risk patients the opportunity to discontinue eculizumab? And, if so, how can we do it safely, given that relapses are unpredictable in terms of both severity and timing? One of the main limitations for the interval extension and discontinuation of eculizumab treatment is the absence of reliable, early (before worsening of renal function, hemolysis, and/or thrombocytopenia) predictors of aHUS relapse.

In the Bouwmeester's study,[9] clinical biomarkers that can be used to predict relapses could not be identified. In only 1 patient could an increase in urine protein-to-creatinine ratio at the last outpatient visit be considered predictive of a relapse. Regular urine checks with a dipstick have recently been proposed as a tool to detect relapses.[S5] However, the positive predictive value of hematuria was low. Indeed, in the 1517 urine determinations in 84 aHUS patients, 90% of the positive tests (defined as hemoglobin $\geq$ 1+) turned out to be false positives and were not associated with a concomitant or subsequent relapse.[S5] Menstrual periods in women of childbearing age, urinary tract infections, bladder stones, and persistent or random hemoglobinuria after aHUS remission all limit the usefulness of hemoglobinuria for screening aHUS relapses, and the false positives may cause patients' anxiety.

In search of biomarkers of aHUS relapses, we recently retrospectively evaluated the sensitivity of an *ex vivo* serum-induced C5b-9 formation test on human microvascular endothelial cells (HMEC-1),[S6] in patients who underwent eculizumab tapering and discontinuation. Elevated C5b-9 formation was observed on unstimulated HMEC-1 exposed to serum from aHUS patients with active disease but not on cells exposed to serum from patients who were on remission. aHUS serum-induced C5b-9 formation on endothelium normalized during

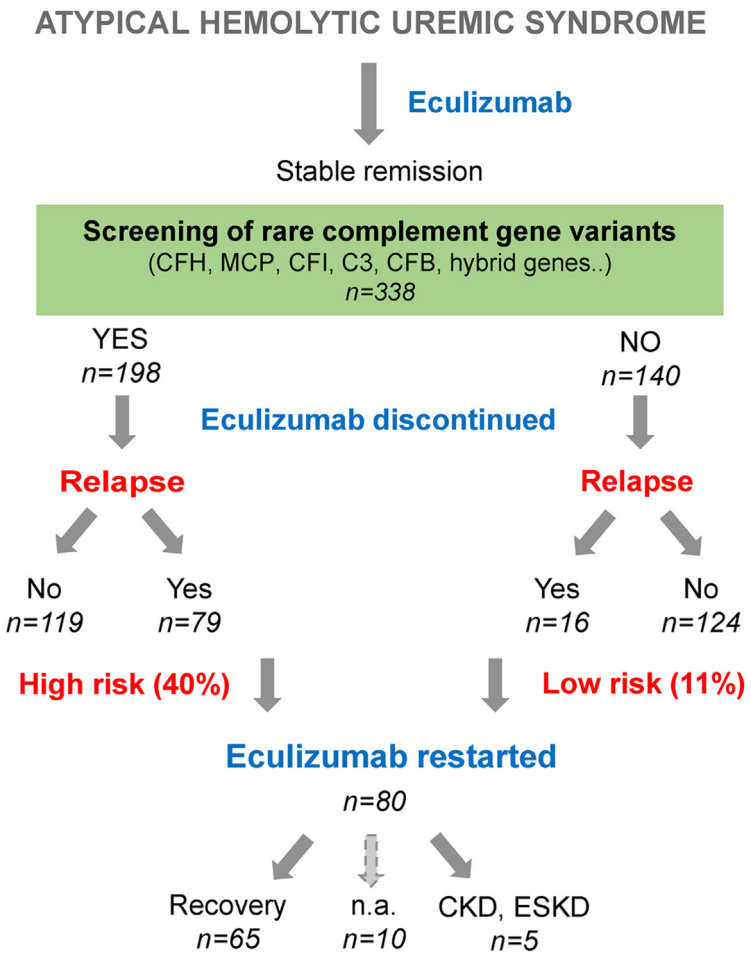

Figure 1. Overview of the outcome of patients with aHUS after eculizumab discontinuation. Published data from patients who were in full remission at the time of discontinuation and who underwent screening for abnormalities in complement genes have been considered.[6-9, S2–S4] CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; MCP, membrane cofactor protein; YES, complement gene variants identified; NO, no gene abnormality identified.

eculizumab treatment.[S7] When the interdose period was prolonged until discontinuation, aHUS relapses occurred in 5 patients; notably, the serum-induced C5b-9 formation test became positive in concomitance with or preceding clinical signs of relapses in all patients.[S7] In contrast, only 6% of patients who maintained stable remission had a positive test anytime during follow-up.[S7]

Identifying predictive biomarkers would be a valuable safeguard for treatment tapering and discontinuation, because it would lead to early reinitiation of eculizumab before full-blown aHUS, and/or would help to identify which patients should maintain treatment because they are at high risk of aHUS relapse.

In this regard, the serum-induced C5b-9 endothelial formation assay may represent an advancement in our ability to diagnose and monitor aHUS activity and individualize therapy. However, the sensitivity and specificity of the test need to be confirmed in a longitudinal trial of eculizumab discontinuation like CUREiHUS,[9] with strict patient selection and clinical and genetic characterization and careful clinical monitoring.

In conclusion, the results of Bouwmeester's study[9] support previous studies that have emphasized the feasibility and social responsibility of controlled eculizumab withdrawal in patients with aHUS (Figure 1). Patients and physicians should be aware of the risk of relapse, especially in patients with pathogenic complement gene variants, during the first year after treatment withdrawal, or in concomitance with triggering events like infections. Early reinitiation of anti-C5 therapy is essential for preserving renal function. Therefore, specific, sensitive, and predictive markers of relapse are needed.

Moreover, we still have to investigate the long-term effects that may be associated with chronic activation of terminal complement even in the absence of clinical signs of relapse.

DISCLOSURE

MN has received honoraria from Alexion Pharmaceuticals for giving lectures, and for participating in advisory boards, and she has received research grants from Omeros, Gemini, Novartis, and BioCryst Pharmaceuticals. GR has consultancy agreements with AbbVie, Alexion Pharmaceuticals, Novartis Pharma, and BioCryst Pharmaceuticals.

ACKNOWLEDGMENTS

The authors are deeply grateful to Kerstin Mierke for English language editing and to Manuela Passera for secretarial assistance. MN was supported by grants from Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), Project ERAPERMED2020-151, GA 779282, and Progetto DDD Onlus - Associazione per la lotta alla DDD (Milan, Italy).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplemental References.

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