Defining Treatment Duration in Atypical Hemolytic Uremic Syndrome in Adults: A Clinical and Pathological Approach

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Abstract: Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) that is driven by uncontrolled activation of the alternative complement pathway, classically in the context of a genetic or autoimmune complement abnormality. Initial guidelines suggested lifelong treatment with the C5 inhibitor eculizumab, which until recently was the only therapy approved by the US Food and Drug Administration and European Medicines Agency for aHUS. However, multicenter observational studies provide compelling evidence that discontinuation of eculizumab, with careful monitoring for recurrence of renal injury, is an option for some patients. Although relapse occurs in 20% to 35% of patients with aHUS after a median of 3 months (range, 1-30 months) following eculizumab cessation, ostensibly irrespective of initial treatment duration, successful rescue with reinstitution of drug has been described in small cohorts if relapse is promptly recognized and eculizumab is immediately re-started. Rates of off-treatment TMA are higher in children than in adults; they are also elevated in those with a personal or family history of aHUS, certain complement mutations or anti–complement factor H autoantibodies, a renal allograft, or extrarenal manifestations of aHUS. Given the complex and unpredictable nature of aHUS, prospective trials defining the optimal treatment duration in diverse settings are required. In the interim, this review—which excludes pediatric patients and hematopoietic stem cell transplant recipients—suggests that eculizumab may be discontinued in some groups of patients; discontinuation should be undertaken on a case-by-case basis and with careful monitoring, following 6 to 12 months of treatment for aHUS that encompasses at least 3 months of normalization of renal function or stabilization of chronic renal disease.

Introduction

The required duration of maintenance treatment with the humanized anti-C5 monoclonal antibody eculizumab (Soliris, Alexion) in atypical hemolytic uremic syndrome (aHUS), a complement-mediated thrombotic microangiopathy (TMA), is unresolved. Advocates for

discontinuing treatment within 6 months after remission induction highlight several concerns. First is the risk for infection, particularly meningococcal meningitis, secondary to blockade of those terminal complement components required for the control of *Neisseria meningitidis* and *Neisseria gonorrhoeae* in adults, as well as several other encapsulated microorganisms in children. Second is the potential for immune side effects of eculizumab. Third is the impaired quality of life related to the need for biweekly intravenous infusions of drug. Fiscal considerations are fourth, given the high cost of eculizumab.[1] The first 2 concerns present a very low risk. The meningococcal meningitis event rate was 0.6 per 100 patient-years in a 10-year study of eculizumab-treated patients with paroxysmal nocturnal hemoglobinuria (PNH).[2] In a survey of 41 patients treated for aHUS, meningococcal meningitis developed in 2 (4.9%), but neither had received adequate prophylaxis with either serotype-B vaccination or antibiotics.[2] A later study identified 2 cases among 87 treated patients (2.3%), but details regarding prophylaxis were not provided.[3] With the possible exception of the rare occurrence of a reversible hepatotoxicity,[4,5] no other known long-term side effects have been linked to eculizumab over nearly 2 decades of use in PNH, including during pregnancy.[6] In terms of convenience, amino acid modifications of eculizumab led to the development of ravulizumab-cmvz (Ultomiris, Alexion), which has a half-life of at least 8 weeks.[7] Ravulizumab-cmvz was approved by the US Food and Drug Administration for the treatment of aHUS in October 2019. It appears that cost considerations are paramount.

In terms of value for cost, there is little debate over the clinical utility of eculizumab in acute aHUS, given the dramatic declines in morbidity and mortality that have been achieved in comparison with interventions based on another major TMA, thrombotic thrombocytopenic purpura (TTP), including plasma exchange.[8,9] In one study, initiation of eculizumab within 7 days of hospitalization—an interval based on the average time required to obtain results of an ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif) test to facilitate distinction between TTP and aHUS—was associated with lower dialysis rates, less time in the intensive care unit, and lower hospitalization costs compared with later initiation of eculizumab.[10] However, in terms of maintenance therapy after induction of a complete clinical remission, one review of eculizumab use for aHUS in the setting of a renal transplant argued that "the cost-effectiveness acceptability curves indicate that lifelong eculizumab therapy seems unrealistic and unacceptable."[11]

How strong are the data supporting a limit to eculizumab treatment in the myriad scenarios accompanying aHUS? An early synopsis of 24 patients who had aHUS treated with eculizumab for 0.4 to 14 months found that hematologic remission and improvement in renal function were achieved in all.[1] Although relapse occurred in 6 (25%) within 6 days to 6 months after drug withdrawal, the remaining 75% remained in remission over 4 to 22 months of follow-up.[1] Given the lack of randomized clinical trials addressing treatment duration, it was concluded that "the outcomes of [such] accumulated case reports are likely to influence practice."[1] Readers have also been directed to "expert opinion."[8]

Data from international aHUS registries have been used as guidance. A 2019 review of 1147 patients in the noninterventional Global aHUS Registry who were treated with eculizumab found a lower TMA rate in those who remained on treatment than in those discontinuing the drug: 3.6 vs 10.7 instances per 100 patient-years, respectively.[3] Limitations of the study, such as selection bias and limited follow-up, were specified. Yet, given the ability to reinduce remission in most individuals with subsequent eculizumab administration, some authors[4,11] concluded that discontinuation of eculizumab could be considered on a case-by-case basis after 6 to 12 months of treatment, including at least 3 months of normalization of kidney function or stabilization of residual chronic kidney disease, with the proviso that allograft recipients and children younger than 3 years be excluded.[12]

The goal of this review is to develop an algorithm by which eculizumab (and, given its noninferiority in comparisons of PNH and aHUS trial outcomes, ravulizumab-cmvz) might be discontinued in specific clinical scenarios. However, I cannot overemphasize the current lack of data from controlled trials, and I encourage practitioners unfamiliar with the use of eculizumab to seek expert guidance when considering discontinuation of treatment. This review is intended to serve all practitioners by providing summaries of the types of information readily available—patient and family histories, clinical laboratory test results, and, via specialty labs, genetic information—as well as pilot assays conducted in research settings, on which experts rely to reach an opinion.

The Role of aHUS Pathophysiology in Decisions Regarding Treatment Duration

The development of aHUS appears to require 2 conditions: (1) preexisting susceptibility factors, either congenital or acquired, that interfere with the ability to regulate activation of the alternate complement pathway; and (2) modulating factors that promote endothelial cell and platelet activation and injure endothelium in the context of complement activation.[13] The latter—suggesting a requirement for the presence of a potent complement-activating condition—could account for the sporadic

development at any age of the overt clinical signs and symptoms of a disorder predicated on a genetic susceptibility; initial episodes have been recognized in a 1-day-old newborn and an 88-year-old adult.[14]

Some two-thirds of aHUS cases are associated with identifiable complement-activating conditions,[13,15] which include the following: infection (notable agents are H1N1 influenza virus [and H1N1 vaccine], adenovirus, cytomegalovirus, human immunodeficiency virus, *Streptococcus pneumoniae*, and Shiga toxin–producing *Escherichia coli* [STEC]); pregnancy; malignant hypertension; autoimmune disorders (particularly systemic lupus erythematosus and systemic sclerosis); surgery; organ and tissue transplant; and malignancy.[13,16] Certain immunosuppressive drugs (calcineurin inhibitors and mammalian target of rapamycin inhibitors), cancer chemotherapeutic agents (gemcitabine, mitomycin C, cisplatin, and the vascular endothelial growth factor inhibitor bevacizumab), platelet antagonists (ticlopidine and clopidogrel), and the extended-release form of oxymorphone can also damage endothelium, activate complement, and unmask aHUS.[13] Even classic TTP[17,18] or hemolytic crises related to sickle cell anemia and cold agglutinin disease[19] may unmask aHUS in a genetically susceptible individual. In the pathophysiology of the former, thrombin, activated in the course of TTP, may serve as a C5 convertase, with the generation of terminal complement components (C5a and soluble [s]C5b-9) and platelet activation.[15,20,21] Heme can also activate complement and generate C5a and sC5b-9, leading to a positive feedback loop between hemolysis and complement activation.[22]

The consequences of such uncontrolled complement activation with the generation of C5a (an anaphylatoxin) and sC5b-9 (a membrane attack complex) include inflammation, platelet activation and aggregation, erythrocyte lysis, and endothelial cell injury, leading to the formation of fibrin microthrombi throughout the microvasculature.[13] Any TMA can be associated with activation of the alternative complement system.[15] It is rare, however, for a TMA to be sustained except when this activation cannot be regulated, as in aHUS.[23]

Determining the Duration of aHUS Treatment on the Basis of Expert Opinion, Case Reports, and Registry Data

The section on aHUS in the American Society of Hematology 2016 Self-Assessment Program (ASH-SAP) states that the current standard of care is to continue eculizumab "indefinitely."[24] However, advocates for limiting treatment duration note that before the approval of eculizumab, a complete hematologic remission could be obtained in a substantial number of patients with aHUS by using plasma infusion or plasma exchange, presumably

because fresh frozen plasma contains 2 soluble regulators of the alternative complement system, complement factor H (CFH) and complement factor I (CFI).[13] Some of these individuals could also be weaned from maintenance plasma infusions.[25] However, the use of plasma had no effect on the development of end-stage renal disease (ESRD) or overall mortality. For example, in one series, 46% of adults required renal replacement therapy or died within 1 month after disease onset. Fifty-six percent of patients died within 1 year, and relapses occurred in 35% of those who survived the initial aHUS episode before ESRD developed, regardless of the use of plasma.[26]

In a long-term follow-up of 52 adults and 35 children who had aHUS treated with eculizumab, TMA event rates during continuous treatment (ON) vs dose reduction or drug discontinuation (OFF) were examined.[27] With a median follow-up of 26.1 months (ON) and 20.1 months (OFF), the TMA event rate was 2.9-fold higher in the OFF cohort than in the ON cohort, with an intermediate value for those whose dose was reduced.[27] These differences might have been even more pronounced if "event" been defined as a change in more than 1 of 3 TMA-defining parameters (platelet count, creatinine level, and lactate dehydrogenase [LDH] level), as required in later studies (Table 1). In groups of selected patients, however, the majority were able to stop drug with no detectable permanent consequences over the median 2-year follow-up, leading to a recommendation to treat for a "sufficiently long period to ensure maximal organ function recovery" and to be certain that the patient can be "monitored closely for signs and/or symptoms of TMA." In addition, something much more intangible is advised: "recognition of the complex and unpredictable nature of aHUS."[27]

In a French study of 108 people with aHUS, none of whom was an allograft recipient, had another underlying condition such as cancer or an autoimmune disease, or was receiving a complement-activating drug, eculizumab was withdrawn in 38 (35%) after a median duration of 17.5 months.[12] During a median follow-up of 22 months, 12 patients (32%) had a relapse, but re-treatment with eculizumab was successful. The duration of initial treatment with eculizumab did not influence the risk for aHUS relapse, given that 3 of the 38 individuals (7.9%) who had received eculizumab for at least 2 years nonetheless had a relapse within 6 months after treatment cessation.[12] Limiting the generalizability of these findings was the fact that withdrawal of eculizumab involved a nonrandomized subset, introducing selection bias.

A multinational observational study of 93 patients, including 67 adults, found that after a median follow-up of 65.7 months, 45% of the patients had discontinued therapy. Of those who discontinued therapy, 50% required re-initiation of eculizumab.[28] All TMA manifestations

Table 1. Definition of an aHUS Relapse After Eculizumab Withdrawal

At least 2 of the following are required:
• Thrombocytopenia (platelet count <150,000/mm³)
• Microangiopathic hemolytic anemia (identified by the presence of ≥2 of the following criteria: hemoglobin level of 10 g/dL, LDH level > upper limit of normal, undetectable haptoglobin, schistocytosis)
• Acute kidney injury (creatinine level > upper limit of normal for age or increased >15% from baseline)
• Renal biopsy showing evidence of an acute TMA (glomerular and/or arteriolar thrombi, double contours, endothelial cell detachment)
In Addition:
• If patient self-monitoring indicates a change in urine characteristics (development of hematuria or proteinuria) or a new rise in blood pressure, a health care provider should be consulted to determine if a relapse is indeed imminent.

aHUS, atypical hemolytic uremic syndrome; LDH, lactate dehydrogenase; TMA, thrombotic microangiopathy.

Source: Fakhouri F et al. *Clin J Am Soc Nephrol.* 2017;12(1):50-59.[12]

occurring during off-treatment periods were identified within the first 30 months after discontinuation.

Safety Considerations in the Discontinuation of Eculizumab

The assumption underlying all treatment interruption and so-called duration-based "restrictive therapy" strategies is that organ function can be rescued by re-initiating therapy in the setting of relapse when patients are not taking drug. However, this hypothesis requires more data because specific concerns exist.

In the multinational study, renal function declined in 40% (14/35) of individuals who discontinued eculizumab vs 23% (11/37) of those who remained on the drug.[28] In addition, renal function was less likely to improve in the patients who discontinued eculizumab than in those who maintained therapy (6% vs 35%), including the 75% of patients who reinstated eculizumab.[28] This raises a concern that is not adequately addressed by existing case reports and observational studies: how long might subclinical TMA activity persist after eculizumab has been discontinued? A trend toward decreased estimated glomerular filtration rate (eGFR) was observed when the patients were off drug, but it was not statistically significant.

The "close monitoring" of patients discontinuing eculizumab relies primarily on self-administered urine dipstick tests for protein and hemoglobin (see point 12, below). However, results of tests to detect these abnormalities, like other fundamental laboratory indicators of a TMA, will be positive only after significant endothelial or renal injury has occurred, which is not ideal.[29]

In an early study from Johns Hopkins, 17 patients with aHUS, most of whom did not have the complement mutations most strongly linked to disease relapse, and only one of whom had a history of TMA, were treated with eculizumab for a median of 3 months (range, 14-545 days). After a median follow-up of 308.5 days, 3 of 15 patients (20%) had experienced a relapse and 2 of the 17 had died.[30] One patient had sepsis related to infected vascular access, presumably a catheter placed for prior plasma infusions. In the other patient, eculizumab had been discontinued after only 2 doses upon recognition of malignant hypertension, even though malignant hypertension appears to be a prominent cause of an aHUS-type complement-linked TMA that can be responsive to eculizumab.[31]

Successful treatment interruption in the long term requires not only close monitoring but also immediate access to eculizumab if a relapse is documented.

Epidemiologic and Pathophysiologic Considerations in Defining the Duration of aHUS Treatment

The 12 parameters discussed below have been proposed by many groups to assist clinicians in reaching evidence-based decisions about discontinuing eculizumab following resolution of an acute episode of aHUS. They are outlined in the algorithm (Figure), with treatment relapse defined in Table 1. The main risk factors for relapse following discontinuation are the following: genetic predisposition; personal or family history of aHUS; relatively severe disease, particularly extrarenal involvement; and a

history of renal allograft. These features are emphasized in the algorithm.

1. Age. In a review of 214 patients with aHUS, the onset of aHUS was recognized as frequently in adults (58.4%) as in those younger than 18 years (41.6%).[26] The likelihood of a severe outcome in untreated disease also did not differ by age; progression to ESRD after a first episode of aHUS was more frequent in adults, but the mortality rate was higher in children.[26] However, in terms of discontinuing eculizumab following the resolution of renal dysfunction and a median treatment duration of 17.5 months, the number of relapses was higher among adults than among children.[12] This was thought to be a consequence of the fact that different types of complement mutations are implicated depending on whether aHUS first occurs in an adult or a child. The issue is still unsettled; a multinational observational study found that off-treatment TMA rates were higher, not lower, in those younger than 18 years.[28]

2. Country of residence. Physicians in many resource-poor nations have been reluctant to recommend discontinuation of eculizumab in pediatric patients before vaccinations have been completed because of the high level of exposure to complement-activating pathogens related to endemic infections and poor sanitation.

3. Personal and family medical history. In the report of the French Registry of Atypical Hemolytic Uremic Syndrome, the rate of relapse following eculizumab withdrawal was much higher in individuals who had experienced at least one aHUS episode before eculizumab use.[12] A Global aHUS Registry study similarly found higher rates of off-treatment TMA in those with a history of multiple TMA episodes.[32] It is critical to recognize that irreversible renal damage may result from repetitive aHUS flares.[12]

Insufficient information is included in most case studies and registry reviews to assess the relative effect of specific complement-activating conditions responsible for promoting relapse following eculizumab withdrawal. However, infection (primarily upper respiratory tract infection, pneumonia, urinary tract infection, and infection following vaccination) and pregnancy appear prominent.[33]

In a review of 851 patients in The Global aHUS Registry, 55% of them adults, a family history of aHUS was documented in 16%.[32] However, family histories are unreliable because aHUS is usually associated with autosomal-dominant mutations characterized by incomplete penetrance.[14]

4. Renal transplant. The extended use of eculizumab in the renal transplant setting has been advocated historically, given that an allograft can be a persistent and potent source of complement activation via anti-HLA alloanti-bodies. The likelihood of aHUS recurrence and graft loss appears to be modified by the genetic background of the host, but the differences related to specific complement mutations were not considered great enough to be useful as a guide to treatment withdrawal.[34] As a result, a 2015 consensus statement, based on a conference of international experts, stated that "transplant patients, especially those who have lost previous allografts, are not good candidates for treatment cessation."[35]

This is an appropriately cautious recommendation in the absence of controlled trials with longer follow-up. However, a multinational observational study found no effect of prior renal allograft on off-treatment rates of TMA,[28] and although the rate of TMA relapse is high in the first few months after transplant, at 12 months it falls to one-sixth of the initial recurrence rate.[11] An observational study from the Netherlands suggested that eculizumab may be withdrawn in cases of renal transplant–associated aHUS if the patient is in clinical remission with well-controlled blood pressure, but that extension of the duration of initial treatment should be considered.[25]

It was recently argued that even prophylactic "induction therapy" with eculizumab in the renal transplant setting should be considered the standard of care only if eculizumab has been shown to be less effective after the onset of a TMA recurrence than if utilized prophylactically.[11] The authors describe 10 patients with a history of aHUS who received a renal allograft without prophylactic eculizumab. Only 1 recurrence (10%) developed over a median follow-up of 2.6 years. However, only living kidney donors had been used, and the patients "strictly avoid[ed] factors that may provoke a recurrence,"[11] although how this was accomplished was not detailed. Acknowledging that irreversible renal damage may result from repetitive aHUS flares, this group did set a limit; those individuals with a third aHUS recurrence in the setting of a renal allograft should receive prophylactic eculizumab for life.[11]

This is still an evolving issue. In an analysis of recent information from The Global aHUS Registry regarding 188 patients with a kidney transplant and at least 1 year of follow-up after their most recent graft, the 2-year eGFRs were significantly better in those who received eculizumab beginning at the time of transplant than in those who received it after the transplant, both in those with a previous aHUS diagnosis (70.2 vs 44.8 mL/min/1.73 m^2) and in those with aHUS diagnosed and treated after the graft (24.2 mL/min/1.73 m^2).[3]

5. End-stage renal disease. Failure to improve renal function should not be used as a rationale for discontinuing therapy in individuals otherwise responding to eculizumab

Table 2. Selected Commercial and University-Based Resources Offering aHUS-Related Genetic Testing[a]

Test Panel Name	Resources	Turnaround Time
aHUS Genetics Panel	Machaon Diagnostics, Oakland, CA machaondiagnostics.com	2 business days
Genetic Renal Panel	Molecular Otolaryngology and Renal Research Laboratories, University of Iowa, Iowa City, IA morl.lab.uiowa.edu	3 weeks
aHUS/DDD Genetic Evaluation	Versiti Blood Center of Wisconsin www.versiti.org	4 weeks

[a] I have personally used these 3 laboratories in evaluating genetic risk factors for aHUS. This information may be useful both in making an initial diagnosis and in deciding on treatment duration.

treatment. Extended follow-up of patients in the initial studies used to support the registration of eculizumab showed continued improvement in the eGFR, with no plateau within 2 years of therapy.[36]

6. Extrarenal manifestations of aHUS. Extrarenal manifestations of aHUS, particularly myocardial and pulmonary involvement, are present in 19% to 38% of patients with aHUS at the time of initial diagnosis.[32] Retinal artery thrombosis with vision loss, bowel necrosis, myocardial infarction, and catastrophic cerebrovascular accidents have also occurred following cessation of treatment. In a French series in which 38 of 108 individuals discontinued eculizumab and 32% of them had relapses, 1 patient had a relapse with pancreatic disease.[12] It is unclear how a patient could be monitored for any of these conditions, and cardiovascular/cerebrovascular complications were dismissed by an international consensus group examining the management of aHUS in children. "Therefore, this problem currently is not demonstrated as a reason for lifelong complement blockade," they asserted.[37] However, an Austrian group stressed the importance of extrarenal involvement in aHUS regardless of age. "Still, the decision on how and when to use and wean eculizumab has to be decided on an individual basis considering renal and *extra-renal perspectives* [italics mine] in combination with the underlying pathophysiology of the affected patient," the authors concluded.[38]

7. Ongoing complement-activating conditions. A patient with aHUS unmasked by any unresolved condition characterized by ongoing activation of the alternative complement pathway—autoimmune disease is one prominent example—logically requires continued blockade of excessive terminal complement component production until such activation is resolved. Less clear is whether induction of a complete remission in a patient with such a condition might still be associated with prolonged endothelial cell activation and the induction of proximal complement components (concerns based on experimental analyses of urine and plasma biomarkers; see section 9),[39] and how that information should influence the length of treatment duration.

8. Complement genetics. Data from many international registries support the use of specific mutations in estimating the risk for relapse following eculizumab discontinuation. Given the importance of these mutations in evaluating an individual patient for treatment discontinuation, I have listed the names of 3 laboratories, 1 commercial and 2 university-based, that I personally have used to obtain such information (Table 2).

Although eculizumab-mediated recovery of renal function was equivalent in patients in the French cohort who had aHUS with and those who had aHUS without identifiable complement mutations, 8 of 11 (73%) with CFH variants and 4 of 8 (50%) with membrane cofactor protein (MCP, CD46) variants had a relapse while off the drug, resulting in odds ratios of 80 and 25, respectively.[12] In contrast, no relapses occurred among the 16 individuals with no detectable mutations.[12] The authors concluded that eculizumab discontinuation appears to be safe in patients with no documented complement gene variants after 6 to 12 months of treatment.

That recommendation is consistent with information in the multinational observational study. The off-treatment TMA rate was higher in patients who had aHUS with complement mutations or anti-CFH autoantibodies than in those lacking such abnormalities (67% vs 48%, respectively).[28] Mutations in *CFH*, *C3*, and the complement factor B gene (*CFB*), or the presence of anti-CFH autoantibodies, were linked to a particularly high risk for relapse, whereas variants in *MCP* or *CFI* were associated with a lesser risk.[28] A retrospective observational study from the Netherlands confirmed the importance of CFH variants in relapse risk; 4 of 8 patients (50%)

with *CFH* mutations had a relapse off treatment vs 0 of 7 patients with mutations in the gene for CFH receptor 1 (*CFHR1*), *CFI*, or *CFB*, or with no identified mutation.[25] A summary of 9 reports in adults and children found aHUS relapses in 31% to 55% of individuals with *CFH* mutations, 50% of those with *C3* variants, and 18% to 52% of those with MCP mutations.[4] However, reliance on the results of genetic testing to predict relapse is likely to be more complex. For example, one report noted that individuals with mutations in exons 17, 19, or 20 of *CFH* appear much more prone to recurrence off therapy than are those with mutations in exons 9 or 15.[40] Less-frequent interactions among complement gene polymorphisms may also play a role.

9. Biopsy. The turnover rate of microvascular endothelium varies markedly, from 47 days to more than 6 years, depending on tissue lineage.[41,42] The possibility that endothelial cell activation, injury, and sC5b-9 deposition might persist in many tissues despite 6 to 12 months of eculizumab treatment is consistent with the continued elevation of endothelial cell activation and injury markers, including thrombomodulin and soluble vascular cell adhesion molecule 1 (sVCAM1), in plasma over 55 weeks of treatment, regardless of mutational status.[39] One group postulated that kidney biopsy might inform treatment duration decisions following resolution of a prior relapse consequent to treatment interruption,[12] but more data are required.

10. Research biomarkers. The value of plasma or urine levels of sC5b-9 as markers for aHUS disease activity or their use in predicting relapse off therapy is unresolved.[43] Eculizumab-based suppression of sC5b-9 to levels found in healthy controls should not be interpreted as a rationale for discontinuing the drug. In a pivotal report by Cofiell and colleagues, eculizumab normalized urinary sC5b-9 and C5a levels within 4 to 6 weeks of treatment, but a marker of proximal complement activation, plasma Ba, remained elevated at week 12 through the end of follow-up at week 55.[39] This persistent elevation in Ba might be thought of as *potential energy* awaiting conversion into the kinetic energy of terminal complement components capable of reinitiating aHUS as soon as eculizumab-mediated blockade of those components is removed. What we do not yet know is how clinically relevant Ba measurements are in terms of relapse frequency, how long past 55 weeks elevated Ba levels persist following treatment cessation, how genetics might influence the clinical importance of such elevated levels, and whether discontinuation of eculizumab is warranted when Ba levels return to baseline.

Our group was able to correlate the kinetics of changes in plasma sC5b-9 and C5a levels with the deposition of sC5b-9 on microvascular endothelial cells in serial cutaneous and jejunal biopsy specimens in a small number of patients with aHUS (these data have not been published). Consistent with the literature on urinary sC5b-9 and C5a, plasma levels fell to the normal range within 4 to 6 weeks after the initiation of eculizumab therapy, but dermal and jejunal deposition of sC5b-9 persisted for at least 1 year of therapy. Similar kinetics have been observed in the kidney in aHUS,[44] and aHUS-type TMAs occurring after renal transplant.[45] In other C5b-9–linked pathologies, such as dense deposit disease and C3 glomerulonephropathy, renal deposition of C5b-9 persisted for more than 1 year despite eculizumab.[46]

11. Additional research assays. As an alternative to stopping eculizumab, decreasing the drug dose or increasing the dosing intervals has been proposed. The half-life of eculizumab is 10 to 12 days, underlying the recommended maintenance schedule of biweekly infusions. The ON/OFF study, previously described, found that drug tapering resulted in significant increases in TMA manifestations in comparison with drug continuation.[27] However, one group suggested that "informed" dose reduction or drug cessation may be possible, on the basis of the outcome of an experimental in vitro assay.[44] Specifically, eculizumab treatment normalized the patient serum–mediated deposition of sC5b-9 on activated, transformed human dermal microvascular endothelial cells tested in vitro. Eculizumab dosing was titrated according to the findings of this assay in 4 patients, with good results.[44]

Other models designed to help dosage adjustment are in development.[47] These assays are currently based on small numbers of patients with aHUS and include few disease controls, but the concept, if validated in clinical trials, could prove valuable in the future to justify dosage adjustments or treatment duration. On the basis of quantitation of circulating C5, one study concluded that "a majority of patients receive substantially more drug than needed for complete C5 inhibition."[48] Reported eculizumab trough levels as high as 700 µg/mL, with an inter-individual variant coefficient of 45%, have been described in many patients on standard eculizumab maintenance, when goals for these levels are actually 50 to 100 µg/mL.[4]

12. Recommendations for follow-up after eculizumab withdrawal. Successful rescue of patients whose disease relapses is predicated on restarting eculizumab very rapidly—in one study, within 48 hours of TMA recognition. However, this may be problematic in a real-world setting.[12] Patients are advised to measure their blood pressure at home and to use dipstick tests for urine protein and hemoglobin
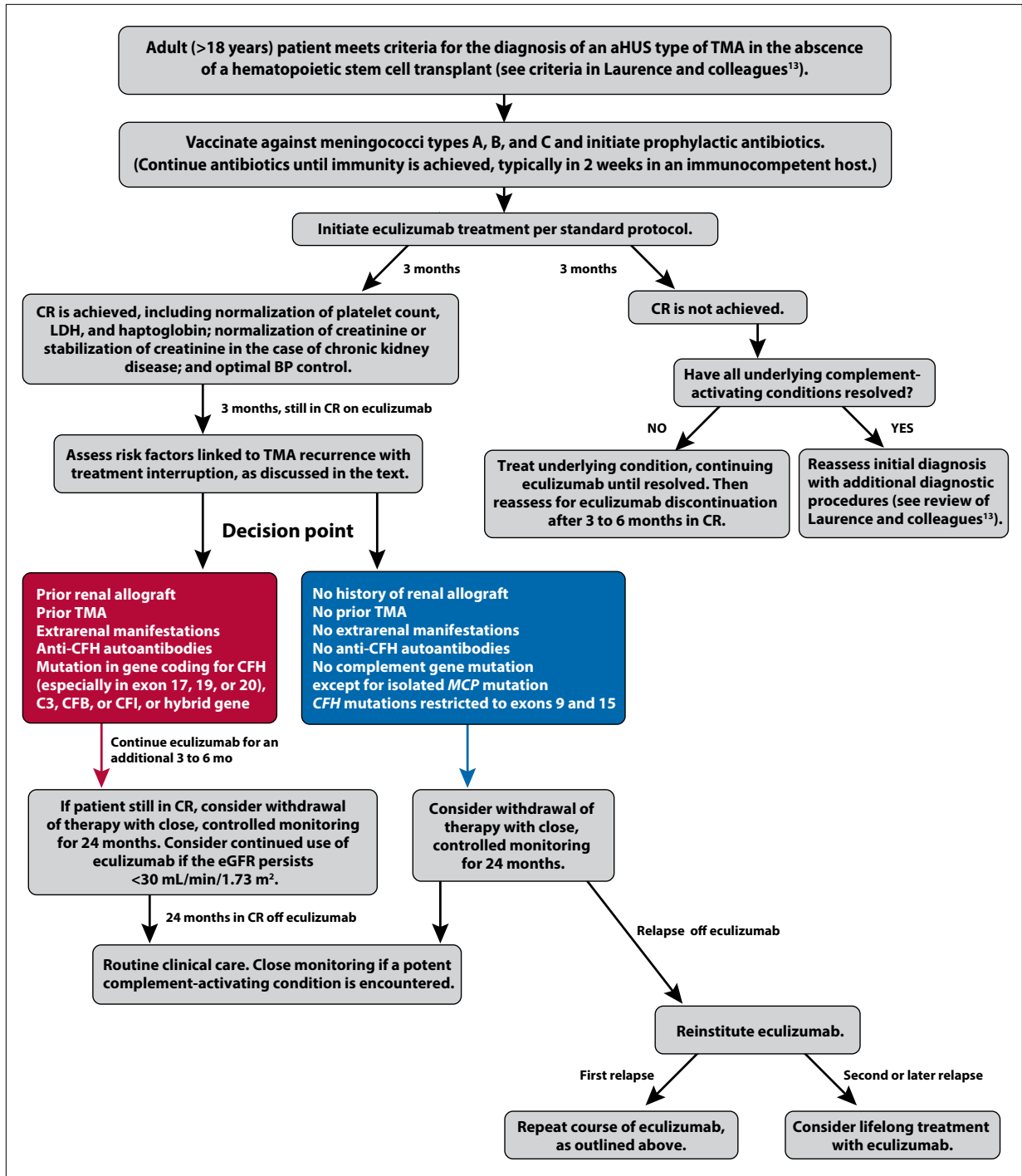
Figure. Algorithm to assist in determining the duration of eculizumab treatment for atypical hemolytic uremic syndrome. Users should refer to the text for details related to each of the branch points outlined here. It is important to emphasize that treatment duration should be considered on a case-by-case basis. Expert opinion should also be sought. Discontinuation of treatment should not be attempted unless appropriate monitoring of the patient is available, along with immediate access (within 24 to 48 hours) to eculizumab should a relapse be documented or suspected (according to the criteria outlined in Table 1). Appropriate monitoring of the patient includes frequent self-checks with urine dipsticks and blood pressure monitoring.

aHUS, atypical hemolytic uremic syndrome; BP, blood pressure; CFH, complement factor H; CR, complete response; eGFR, estimated glomerular filtration rate; ESRD; end-stage renal disease; LDH, lactate dehydrogenase; MCP, gene for membrane cofactor protein; TMA, thrombotic microangiopathy.

3 times per week.[4] One group suggested close monitoring with clinical access for the first year off therapy: collection of blood for hemoglobin, platelets, haptoglobin, LDH, and creatinine, and collection of urine for protein and hemoglobin, every 2 to 4 weeks for the first 4 months and every 2 months thereafter for 1 year.[25] Others advocate for an extension of the every-2-month follow-up for another year. Patients are advised to report signs of infection, malaise, fever, hematuria, edema, oliguria, paleness, or an increase in blood pressure. Among patients with renal transplants, calcineurin inhibitor levels were monitored, statins were given to those with abnormal cholesterol or labile hypertension, and blood pressure was closely controlled.[25]

Conclusions and Future Directions

The introductory section poses an important question: can one prospectively identify those individuals who should be able to discontinue eculizumab safely after 6 to 12 months of therapy and define how to monitor them, so that they can be rescued by the reintroduction of drug if they do have a relapse? Unfortunately, this question does not yet have a clear answer. In the absence of controlled trials, however, useful guidelines have appeared that are summarized here and in the Figure.

The fact that 90% of all aHUS relapses occur within 1 year after discontinuation of eculizumab supports the use of eculizumab therapy for a minimum of 6 to 12 months. This should encompass at least 3 months of treatment after normalization of the serum creatinine or stabilization of a chronic kidney disorder, which provides an opportunity for further improvement in renal function in those patients with active recovery. A period beyond 12 months should be considered if a *CFH, C3, CFB,* or *CFI* mutation is documented; if hybrid genes, *CFH* gene rearrangements, or anti-CFH autoantibodies are present; or if the patient has a history of a prior aHUS episode or renal transplant. If aHUS has been diagnosed in the context of a recognized complement-activating condition, eculizumab should be continued until that condition has resolved—for example, successful treatment of an autoimmune disorder or infection.

Following eculizumab discontinuation, careful monitoring per the guidelines summarized here is mandatory, together with immediate access to eculizumab should a relapse be discovered. I am currently involved in designing a decision tree, based on international expert opinion, to further inform clinicians on how to determine eculizumab treatment duration on a case-by-case basis. What is ultimately required was well stated in a recent commentary: "The balance between the ethical obligation to offer patients the best treatment, drug affordability, and patient risk requires a strict and rigorous prospective international research collaborative effort to provide proof and guidelines for aHUS future management."[3]

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