Treatment discontinuation in atypical hemolytic uremic syndrome (aHUS): A qualitative study of international experts' perspectives with associated cost-consequence analysis

Evi Germeni
University of Glasgow
Jacie Cooper
Avalon Health Economics LLC
Andrew Briggs
London School of Hygiene & Tropical Medicine
Jeffrey Laurence
jlaurenc@med.cornell.edu
Weill Cornell Medical College

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Abstract

Background

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening thrombotic microangiopathy (TMA) related to congenital mutations impeding control of the alternative pathway of complement. Following approval of the complement C5 inhibitor eculizumab by the European Medicines Agency and the US Food and Drug Administration, initial guidelines suggested lifelong therapy. Yet, growing evidence indicates that discontinuation of eculizumab, or its long-acting form ravulizumab, is possible for many patients. This mixed-methods study sought to explore international experts' perspectives and experiences related to treatment duration in adult patients with aHUS, while also estimating the financial and potential health consequences of early discontinuation.

Methods

Between January and December 2023, we conducted 10 qualitative interviews with experts in the treatment of aHUS, based upon which we constructed a quantitative decision tree, designed to estimate time on treatment and treatment- and disease-related adverse events.

Results

Thematic analysis of the interview data identified four main themes: (1) Concerns and prior experience; (2) High-risk *vs.* low-risk groups; (3) Patient preference and adherence; and (4) Funding for monitoring and re-treatment. Although most interviewees were in favour of considering treatment discontinuation for many patients (citing the high cost, burden, and potential side effects of lifelong treatment as key reasons), a prior negative experience of discontinuation seemed to make others more reluctant to stop. Deciding which patients required lifelong treatment and which not involved consideration of a wide range of factors, including patient- and system-related factors. Cost-consequence analysis demonstrated the financial savings associated with early treatment discontinuation at the expense of increased risk of recurrent TMA events. Close monitoring for these events had the potential to minimise any long-term injury, primarily renal, with an estimated one event per 100 patient years. For patients at high risk of TMA and with poor adherence to monitoring, rates of renal injury rose to three events per 100 patient years.

Conclusions

aHUS treatment protocols are changing globally in response to new clinical evidence. Against this backdrop, our mixed-methods study provides compelling evidence on the complexity of factors influencing treatment discontinuation decisions in aHUS, as well as the financial and health consequences of early discontinuation.

Background

Atypical hemolytic uremic syndrome (aHUS) is a rare, life-threatening form of thrombotic microangiopathy (TMA), characterised by microangiopathic hemolytic anemia, thrombocytopenia, acute kidney injury, and other organ involvement (1–3). To date, the diagnosis must be made clinically, following exclusion of other TMA causes (4). The annual incidence of aHUS is estimated to range between 0.23 and 1.9 per million population, depending on region and age group (5), but this is thought to be a significant underestimate (1). Although originally assumed to be a pediatric disorder, almost half of all cases occur in individuals aged over 18 years (6). Primary aHUS, accounting for an estimated 70% of all aHUS, arises from congenital abnormalities of complement-related proteins that allow uncontrolled complement activity (1). Secondary aHUS can be a consequence of a variety of clinical scenarios, including pregnancy, malignancy, autoimmune disease, infection, and certain prescription medications (7). Although also linked to marked complement activation, identifiable complement mutations occur in only 5–20% of cases (8, 9), rendering differential diagnosis, treatment, and treatment duration decisions challenging.

For many years, plasma infusion or exchange was the sole therapeutic option for patients with aHUS. However, plasma therapy served only as a temporising measure, often improving peripheral hemolytic abnormalities but having no effect on overall survival or development of end stage kidney disease (ESRD) (1, 10). In 2011, the introduction of the humanized anti-C5 monoclonal antibody eculizumab radically transformed the landscape of aHUS management, with most patients responding to C5 inhibition and the risk of ESRD dropping to 10–15% (11–13). Lifelong treatment with eculizumab had since become the standard of care, mainly owing to concerns about the risk of aHUS relapses and further kidney injury. In 2019, the longer-acting C5 inhibitor ravulizumab was also approved for aHUS in the United States and, subsequently, in other countries (14). Ravulizumab has the same mechanism of action as eculizumab, but has a weight-based dosage regimen and requires less frequent maintenance doses (once every 8 weeks *vs.* once every 2 weeks), therefore reducing infusion burden and associated adverse events (15–17).

Despite its efficacy, however, long-term complement inhibition therapy comes with an enormous financial cost, while also subjecting patients to an increased risk of Neisseria infections, particularly meningococcal meningitis, of ~ 0.5% per year despite vaccination, and the burden of lifelong intravenous infusions (1, 18). These factors have prompted consideration of when and for whom treatment discontinuation might be considered, and there are currently several observational studies suggesting that many patients can be safely removed, provided that they are carefully monitored for recurrence of kidney injury (19–23). This mixed-methods study sought to meaningfully add to this growing evidence base, by systematically exploring international experts' perspectives and experiences of treatment discontinuation in adult patients with aHUS, while also estimating the financial and potential health consequences of early discontinuation.

Methods

Between January and December 2023, we conducted a sequential mixed-methods study (24), comprising of 10 qualitative interviews with international aHUS treatment experts, based upon which we constructed a quantitative treatment decision tree. Study procedures were reviewed and approved by the Biomedical Research Alliance of New York LLC Organizational Review Board and the Weill Cornell Institutional Review Board (Study Protocol: 21-07023785).

Expert interviews

A list of aHUS treatment experts was compiled based on: (a) prior familiarity to the principal investigator (JL), who is an internationally recognised expert on the treatment of aHUS; and (b) scope of knowledge, documented by recent publications and abstracts indicating familiarity with under-recognized aspects of an aHUS presentation that may impact treatment duration decisions (e.g., post-partum HELLP (hemolysis, elevated liver enzymes, low platelets), anti-phospholipid syndrome, malignant hypertension). A total of 25 experts were contacted via e-mail by the first two authors (EG and JC) and were asked to participate in an online, qualitative interview. Among those, 8 failed to respond and 7 declined to participate. Common reasons for declining included: not treating adult patients (i.e., working only with pediatric populations), not currently invested in the treatment of aHUS, and lack of time. Our final sample consisted of 10 aHUS treatment experts (5 hematologists and 5 nephrologists) based in the United States, Canada, and Europe (Table 1). The identity of the participants was not revealed to the principal investigator.

Table 1
Participant characteristics (n = 10)

Characteristic		No of participants
Gender	Male	6
	Female	4
Specialty	Hematology	5
	Nephrology	5
Country	USA	4
	Germany	2
	Italy	1
	Spain	1
	UK	1
	Canada	1

Expert interviews were conducted via the Zoom video conferencing platform by the first two authors (EG and JC), who have considerable experience in qualitative research. All participants were in private rooms,

either at work or at home, with no one else present at the time. Prior to each interview, details about how data would be collected, analysed, and used were discussed, and signed informed consent was obtained. Data were collected using a semi-structured interview guide, which sought to elicit participants' views and experiences of: (a) management of "straightforward" aHUS cases; (b) management of "challenging" aHUS cases; (c) treatment monitoring and management of relapse; and (d) considerations guiding treatment discontinuation decisions. Questions included in the interview guide are shown in Table 2. Although all participants were asked the same set of main questions, they were also encouraged to raise issues that may not have been addressed in the discussion and they considered important. The average duration of the interviews was 28 minutes (range 17–45 minutes). No follow-up interviews were conducted.

Table 2
Questions included in the interview guide

Topic	Main questions and probes
Introduction	First of all, could you tell me a bit about yourself? *Probes*: • How many adult patients with aHUS do you typically treat in a year? • What are the main challenges in treating these patients? • How are treatment decisions typically made in your department?
Management of 'straightforward' cases	If I asked you to give me an example of a 'straightforward' case that you treated recently, how would this look like? *Probes*: • What made this case straightforward? • How long was the patient left on treatment? • How often do you have cases like this? • Is this how you typically manage such cases?
Management of 'challenging' cases	Looking back to your career so far, what would you say was the most 'challenging' case of an aHUS patient that you have treated? *Probes*: • What made it so challenging? • How long was the patient left on treatment? • How often do you have cases like this? • Is this how you typically manage such cases?
Treatment monitoring and management of relapse	Could you tell me a bit about the monitoring process and your approach to the management of relapse? *Probes*: • How often do you monitor the patient during treatment? And after discontinuing treatment? • How common is it for a patient to relapse after treatment discontinuation and what do you do in such a case? • Based on your experience, what are common risk factors influencing relapse rates? What are common relapse consequences?

Topic	Main questions and probes
Considerations guiding treatment discontinuation decisions	In general, what factors do you take into account when deciding to discontinue treatment? *Probes*: • If I asked you to rank all the factors that you've mentioned in terms of importance, would you be able to do so? • Are there any non-clinical factors that you typically consider? • Is mutational analysis readily available to you? How long does it take to get the results? How heavily do the results weigh on a treatment duration decision? • What kind of tools or types of evidence do you consider when deciding to discontinue treatment? • How do patients typically react when hearing about the discontinuation of their treatment?
Wrap-up	[Interviewer provides a brief summary of the discussion and asks for verification] Is there anything else that you feel is important to mention?

With participant permission, all interviews were recorded and automatically transcribed using the Otter.ai software. Transcripts were checked against the recordings and corrected where necessary. An inductive thematic approach was used for the analysis of the data (25). Experts' perspectives on the treatment of aHUS were coded, with similar codes grouped together to form broader categories and then initial themes. Ongoing refinements were made based on further examination of data summaries and transcripts, and discussions among the team. Final themes were organised in such a way as to create a coherent narrative from collected data.

Cost-consequence analysis

A decision tree was developed based on the results of the expert interviews and an existing treatment flowchart described by Laurence (20). The decision point was assumed to be the point at which a patient has been stabilized on complement therapy (eculizumab or ravulizumab), which could be somewhere between 3 months and one-year following stabilization/remission of disease based on clinical opinion and patient characteristics.

The decision tree developed deals with the first year following the decision to withdraw treatment and compares the expected outcomes with a decision to maintain treatment. Four outcomes are considered:

1) Months on treatment (treatment cost)

2) Cases of TMA that are resolved without renal injury

3) Cases of TMA that lead to long-term renal damage

4) Treatment-related cases of meningitis.

The decision tree is presented in Fig. 1 and shows the comparison to discontinue with the option to continue treatment over a 12-month period. The following assumptions are used for patients continuing on treatment:

- Patients are still at risk of a TMA event, but these occur at a lower frequency because of treatment at an estimate 3.6 events per 100 patient years (26).
- TMA events that do occur on treatment resolve without long-term renal injury.
- There is an increased risk of infection associated with treatment, but this is small at an estimated 0.6 cases of meningitis per 100 patient years of treatment (27).

Where treatment is withdrawn, the following assumptions apply:

- There is an immediate risk of relapse following treatment discontinuation estimated to occur in 20% of patients, rising to 40% in high-risk patients (21, 22).
- For patients who experience an immediate relapse, long-term treatment is re-initiated.
- TMA events occur in patients off treatment at a higher rate than on-treatment estimated as 10.7 events per 100 patient years off treatment (26, 28).
- With adequate monitoring, the majority of these events are resolved by re-initiation of treatment without renal injury, but in a minority of cases, estimated to be 10%, poor monitoring leads to late treatment of the TMA resulting in long-term renal damage.
- Without treatment the risk of meningitis infection is negligible.

For the purposes of keeping the decision tree model simple, relapses following withdrawal of treatment are assumed to occur immediately and TMA events are assumed to occur midway through the year and assumed to require 6 months of complement inhibitor therapy for those whose treatment was discontinued.

Results

Expert interviews

Four main themes were identified from the analysis of the interview data: (1) Concerns and prior experience; (2) High-risk *vs.* low-risk groups; (3) Patient preference and adherence; and (4) Funding for monitoring and re-treatment (Fig. 2). Each theme is presented in detail below, along with representative participant quotes highlighting and supporting key aspects of the theme.

Concerns and prior experience

Expert views on the optimal treatment duration for adult patients with aHUS largely fell into two camps: either keeping patients on treatment indefinitely to avoid relapse or removing certain patients from treatment after the first three or six months (duration varied based on country and protocol followed). Although the vast majority of interviewees were in favour of treatment discontinuation – conditional on certain criteria being met, such as improved renal function or resolved trigger, if known, for aHUS development (e.g., pregnancy) – a prior negative experience of discontinuation seemed to make others more reluctant to consider the possibility of stopping: *"In my own personal practice, it has been really exceedingly rare for me to recommend that a patient can discontinue their anti-complement therapy for their aHUS. I have one woman who had postpartum development of aHUS. And she was on therapy for three or four years, she was doing great, she really wanted to come off. It was right around the same time that the Italian data came out about that you could potentially stop people. And she came off and she had a recurrence about six months after she stopped. So, she's back on now. So, you know, I think that, in part, it has to do with your patient population. But I think, in part, it also has to do with respecting the potential underlying polymorphism or other abnormalities in complement regulatory proteins that are not going to go away and that are going to continue to put patients at risk"* (Participant 4, USA).

Among experts supporting treatment discontinuation, concerns about the burden, high cost, and potential side-effects of lifelong treatment were often cited as key reasons: *"You know, I often use the analogy of a chest infection. If you have a chest infection, you go on antibiotics. You might get another chest infection in two years' time, but you don't stay on antibiotics to prevent it from happening two years later. You treat it when it flares up. And I see us moving in this country into that type of protocol for patients with aHUS, where we treat for a flare, and for a period following that to allow adequate establishment of remission, but then those patients will stop. Now, there may be some patients who just flare and flare and flare, and you think, you know, actually this is not working, and we just put them on it and park them on it long-term. But, you know, if you're 28 years old and you have your first episode of aHUS and we treat it, if it goes into remission, it could be another 28 years before you get another one. And you'll be on treatment for 28 years unnecessarily. With both the cost and the additional risk of meningococcal sepsis for that period, unnecessarily… So, I think that carrying on treatment indefinitely, blindly in all patients, is to the detriment of a significant proportion of patients because of the burden and risk of treatment"* (Participant 5, UK). In addition, emerging evidence and a growing international consensus that lifelong treatment is not necessary for all patients, were also frequently mentioned: *"In general, I think all experts now agree that when there are no pathogenic barriers, mutations, in complement genes, you can be confident about eculizumab discontinuation, because the risk of relapses is low. There are prospective studies now, particularly this wonderful study from the French group, showing these differences in the risk of relapses according to the presence or not of a genetic mutation"* (Participant 1, Spain).

High-risk vs. low-risk groups

Deciding which patients required lifelong treatment and which not, typically involved the consideration of many factors, including: patient age at first episode (raised by 9/10), family history of prior TMA (4/10), disease severity at presentation (4/10), previous relapse episodes (1/10), rapidity of eculizumab response

(2/10), improvement in kidney function (10/10), chronic kidney disease stage (5/10), presence of renal transplant (9/10), extra-renal manifestations (1/10), as well as presence of mutations conferring a high risk of recurrence (9/10): *"People where I would be somewhat more reluctant to stop, because the relapse rates are higher than other patients, are people with, you know, the stronger or more pathogenic complement mutations, such as a factor H, or C3, or a factor I mutation… Also, people who have already lost a kidney. Or if they're running on a renal transplant, I'm more reluctant to stop. And I will often not stop in those cases. And finally, people who were diagnosed very young, like, you know, the kid who had the first episode at the age of 2 is different from the woman who has it at the age of 55. These are typically the patients that I will steer away from discontinuation. You're more cautious with those patients. But these are very few cases, most of my patients do stop"* (Participant 9, USA).

Although the results of mutational analysis weighted heavily on participants' treatment and discontinuation decisions, these were not considered in isolation: *"Our general approach is we'll send complement genetics with next generation sequencing right from the beginning and, hopefully, we'll have that within about four to six weeks from the send-out. So, by the time we get to a point where we would be thinking about stopping, we have that information. So, our general approach is, if they don't have a mutation, those would be the patients where we would be more comfortable in stopping. Now, that said, they have to have shown complete hematologic response, we want to hopefully see also complete kidney improvement, or at least stability, for at least a couple of months, and no evidence of extra-renal manifestations of the disease, as we want to make sure that they're very comfortable and stable at that point. For patients who do have an identified genetic mutation, we will typically continue longer term, at least for a year"* (Participant 10, Canada).

Patient preference and adherence

Apart from clinical factors described above, all participants highlighted the crucial role that patient preference and adherence played in their treatment and discontinuation decisions: *"With almost everybody we have the discussion, 'do you want to stop or not'? And, in most cases, the discussion is actually quite well received. There is a minority of patients, I think I'd say 10 or 20%, who do not want to hear about it and with those we will continue treatment, because the patient has to be comfortable with the decision. Because it comes with fairly close monitoring after that. But the majority are very open to it. I think it also depends on your relationship with the patient. If they have confidence that you're going to monitor them, that's going to be okay, most of them are willing to consider stopping, particularly in the eculizumab era, when people were getting infusions every two weeks. After a while they got tired of that and wanted to see if they could go without it. At least in my experience. I've had less of that with ravulizumab because, you know, once every two months they say, 'ok, I could do this longer"* (Participant 9, USA).

Based on experts' accounts, patterns of patient preference seemed to vary according to: patient age and disease severity (i.e., older patients and patients with aggressive aHUS were typically more afraid to stop), access to ravulizumab (i.e., patients were more willing to continue treatment in cases where ravulizumab was available), and existing protocols in each country (i.e., in countries, such as the UK, where lifelong

treatment is the current standard of care, patients were perceived as more reluctant to stop, whereas in countries that had already adopted a time-limited protocol, patient requests for stopping were reported to be more frequent): *"I think part of what's happening now is that patients themselves are hearing that some patients are having successful discontinuation. So, even those patients who have genetic mutations are asking to stop, or they're bringing that up as a treatment decision. And it's never an absolute 'yes' or an absolute 'no' for patients if they are aware of that potential risk. Even if they do have a known mutation, we'll stop it. You know, everybody's going into it eyes wide open, and we monitor them very closely with blood work"* (Participant 10, Canada). Patient adherence to monitoring, which typically included frequent self-checks with urine dipsticks and blood pressure monitoring, was seen as a decisive factor for treatment discontinuation, especially in cases where close monitoring was not always possible: *"But then you need a very compliant patient who really swears that when they feel bad, or they have any kind of infection, or any problem, that they will do urine sticks or go to the doctor to draw blood. Because they're all very far away, they can't come to me, I don't have the capacity to do the regular routine work-up"* (Participant 7, Germany).

Funding for monitoring and re-treatment

There was a consensus that immediate access to treatment (i.e., within 24 to 48 hours), should a relapse be documented or suspected, was a prerequisite for reaching a discontinuation decision. This, however, was not without challenges and several experts narrated instances of having to 'negotiate' or 'convince' decision-makers for funding of monitoring activities and re-treatment: *"The benefit with our programme with the Ministry of Health is that we were able to convince them to give us what they call 'background funding'. So, if we do stop, it's still there and we don't have to go through the initial approval process again. So, if there is evidence of recurrence of disease, even just on labs and not clinically, we can start the drug very quickly again, and we can hopefully prevent any long-term outcomes"* (Participant 10, Canada). Broader issues of how health care systems are supporting off-treatment monitoring were also raised: *"I think the problem is that health systems are very used to monitoring patients who are on a treatment... What's less clear is monitoring patients who are off treatment, and how health care systems do that. Because if anything, if you think of an aHUS patient, they're more at risk off their treatment than they are on treatment. But you can easily get funding to monitor lytic activities, whatever, once the patient is on treatment. They stop that treatment, you put them into a more at-risk position. And then you got to say, 'well, how is that going to be funded?'. So, it's getting the commissioners to think slightly differently about this. And what you need to do is you actually need to take some of the funding that was used for the drug, whilst the patient was on, to move that into monitoring protocols, which will be actually far cheaper, better for the patient in many, many cases, but not free of cost. And I think there is an issue there that needs to be addressed at a systems level about monitoring people not on treatment. And that is something that we are negotiating at the moment about how we do that, because particularly in a centralised system like ours, if we are making a decision to stop somebody, and therefore taking clinical responsibility for that decision, we need to be able to monitor that patient adequately"* (Participant 5, UK).

Cost-consequence analysis

Applying the decision tree of Fig. 1 gives the results presented in Table 3 for a one-year period following cessation of treatment compared to continuation of treatment. The model predicts that by 12-months after the decision to discontinue treatment 21% of subjects will have been returned to long-term treatment, with an average treatment period of 2.9 months over the course of the year. Of patients discontinuing, 8% are predicted to have a TMA that resolves without long-term renal injury compared to just 4% in the group that continues treatment. However, 1% of patients are predicted to experience a TMA event that results in renal damage compared to no patients in the treated group. By contrast, patients on-treatment are at risk of serious infections such as meningitis compared to patients off-treatment, with the risk approaching 1%.

Table 3
Consequences of stopping versus continuing treatment over a 12-month period

	Long-term Tx	Months Tx	TMA resolve	TMA damage	Meningitis
Stop	21%	2.9	8%	1%	0%
Continue	100%	12.0	4%	0%	1%

The results of Table 3 are based on expected event rates for an “average” adult patient with aHUS. However, it is clear from the expert interviews reported above that treating physicians are concerned with high-risk patients and with adherence to monitoring once off treatment. Two scenarios for the basic model are therefore explored. In the first, the underlying risk of a TMA/relapse is doubled to reflect higher than average risk of poor outcomes for some types of patients (22), including those with prior experience of TMA outcomes and/or a genetic trigger for their aHUS condition (primary aHUS). In the second scenario, the proportion of TMAs assumed to cause damage is doubled representing a situation where poor adherence to a self-monitoring protocol results in late presentation of the TMA with consequent higher risks of organ damage.

The results of these two scenarios, plus the scenario where high risk and poor adherence to self-monitoring occur together are presented in Table 4, which shows that the impacts of these scenarios are relatively modest. The key outcome of TMA resulting in damage doubles under each scenario to 2% of the off-treatment group, rising to 3% if the two conditions occur together.

Table 4
Scenarios relating to risk of TMA and adherence with self-monitoring

	Long-term Tx	Months Tx	TMA resolve	TMA damage	Meningitis
High risk of TMA					
Stop	41%	5.6	14%	1%	0%
Continue	100%	12.0	7%	0%	1%
Poor adherence to self-monitoring					
Stop	22%	2.9	8%	2%	0%
Continue	100%	12.0	4%	0%	1%
High risk of TMA and poor adherence to self-monitoring					
Stop	43%	5.6	13%	3%	0%
Continue	100%	12.0	7%	0%	1%

Discussion

aHUS treatment protocols are changing globally in response to new clinical evidence. This mixed-methods study, comprising of qualitative interviews with international aHUS treatment experts and a quantitative decision tree analysis, sought to inform optimal treatment duration guidelines for adult patients with aHUS. The qualitative study is the first to systematically explore the complexity of factors influencing treatment discontinuation decisions in adult patients with aHUS. Our results suggest that, although the majority of interviewees were in favour of treatment discontinuation (citing the high cost, infusion burden, and potential side-effects of lifelong treatment as key reasons), a prior negative experience of discontinuation seemed to make others more reluctant to stop. Deciding which patients required lifelong treatment and which not, involved the consideration of a wide range of factors, including not only clinical (e.g., presence of mutations conferring a high risk of relapse), but also patient- and system-related factors (e.g., patient adherence to monitoring, availability of funding for re-treatment).

The simple treatment duration decision tree presented in Fig. 1 estimated the potential reduction in time off treatment for an average adult aHUS patient, as well as the potential adverse risks of events for both treatment (serious infection such as meningitis) and discontinuing treatment (increased risk of TMA and resulting renal damage). It is clear that, for patients with aHUS, the risk of TMA, when off treatment, is increased relative to being on treatment (28). Yet, with close attention to self-monitoring, re-initiation of anti-complement therapy can resolve the TMA with very little risk of long-term kidney damage. While this encourages the consideration of treatment discontinuation, other long-term studies note the poorer kidney outcomes for those discontinuing anti-complement therapy compared to those remaining on treatment (29).

The close monitoring requirements of treatment discontinuation relies primarily on the self-administration of urine dipstick tests, along with physician visits for blood workup in the event of infection episodes (20). Since these tests detect kidney damage after it has occurred, they are less than ideal and require prompt re-initiation of treatment to reverse kidney damage. To date, much of the concern about high-risk patients has been related to the rate of TMA/relapse, but an alternative definition of a high-risk patient might consider those whose kidney function is already compromised (e.g., stage IV CKD patients) and for whom further renal injury could result in the need for dialysis or transplantation.

Although a very serious condition, the incidence of meningitis among those taking anti-complement therapy (including for paroxysmal nocturnal hemoglobinuria) is low (27) and outweighed by the benefits of reduced TMA events. The principal benefits of discontinuation, therefore, is patient convenience in terms of no longer requiring infusion and the financial benefits (to the system and potentially the patient in the form of co-pays) of discontinuing what is a very financially burdensome therapy. The yearly cost of eculizumab in the US is circa $600,000 including administration, though this can be reduced by approximately 1/3 with a switch to ravulizumab, due largely to the reduced dosing schedule from 2-weekly to 2-monthly (30). Nevertheless, this circa $400,000 cost of ravulizumab is still a huge burden and the model here shows this could be reduced by a further 79% (59% for high-risk patients) to circa $80,000 ($160,000) by discontinuing therapy in those that remain in remission.

The main limitation of the decision tree approach to treatment duration was to limit the analysis to the first-year post discontinuation when anti-complement therapy is potentially lifelong. The event rates and financial consequences identified in this first year could form the basis of a longer-term extrapolation model, similar to that conducted by Wang and colleagues (30). Yet, it should be clear that any such extrapolation model would simply project the identified annual events and savings into the future while the subjects remain alive. With potential savings of circa $320,000 per year for the average patient, any lifelong model would predict many millions of dollars-worth of financial savings over subject lifetimes, with a similar annual risk of adverse events.

Conclusion

aHUS treatment protocols are changing globally in response to new clinical data, permitting a more informed approach to risk *vs.* benefits in discontinuation of therapy. Clinical decision analysis is one tool allowing decision makers to apply evidence-based approaches to make more objective drug termination decisions. Our mixed-methods study provides compelling evidence as to the complexity of factors influencing treatment discontinuation decisions in aHUS, including recognition of groups at high *vs.* low risk for relapse, the value of shared decisions with patients involving the necessity of adherence to close monitoring, and the financial and health consequences of early discontinuation.

Abbreviations

aHUS

Atypical hemolytic uremic syndrome
TMA
Thrombotic microangiopathy
EMA
European Medicines Agency
FDA
Food and Drug Administration
ESRD
End-stage kidney disease
HELLP
Hemolysis, elevated liver enzymes, low platelets

Declarations

Ethics approval and consent to participate

The study was approved by the Biomedical Research Alliance of New York LLC Organizational Review Board and the Weill Cornell Institutional Review Board (Study Protocol: 21-07023785). Written informed consent was obtained from all experts participating in the interviews.

Consent for publication

The consent process involved informing all participants that interviews would form the basis of a publication and that no identifying information would be used.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to the conditions stated at the time of participant consent, but are available from the corresponding author on reasonable request with the relevant permissions and agreement of the Biomedical Research Alliance of New York LLC Organizational Review Board and the Weill Cornell Institutional Review Board.

Competing interests

AB and JL have received consultancy payments from Alexion Pharmaceuticals in addition to the funding reported here.

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Authors' contributions

JL and AB conceived the study. EG and JL designed the qualitative study. JC and EG conducted the interviews. AB and JC constructed the decision tree. EG analysed the qualitative data and wrote the first draft of the manuscript. All authors provided critical input on data analysis and manuscript preparation. All authors read and approved the final version of the manuscript.

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Figures

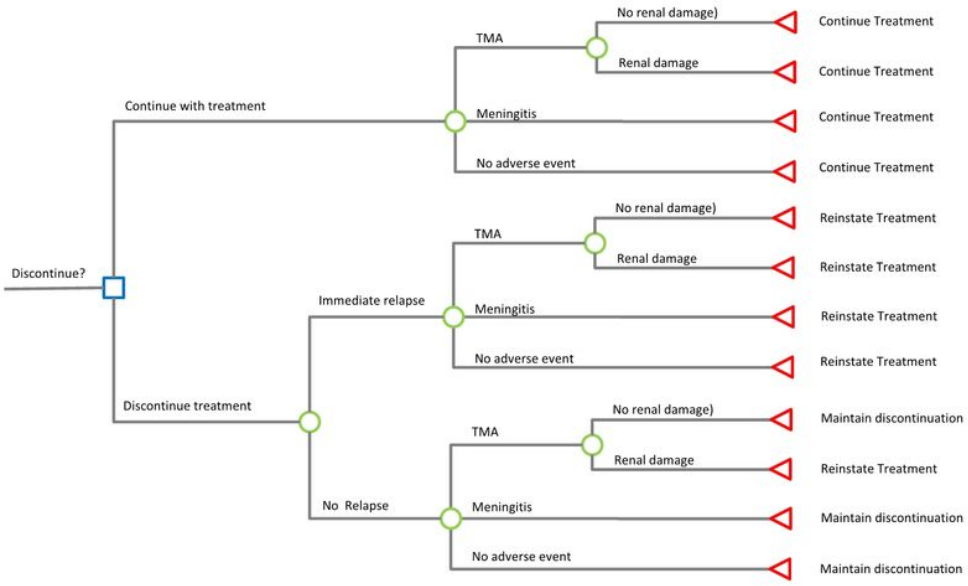

Figure 1

Decision tree comparing the decision to discontinue treatment versus continuation of therapy over 12-months

Figure 2

Main themes identified from the qualitative data analysis