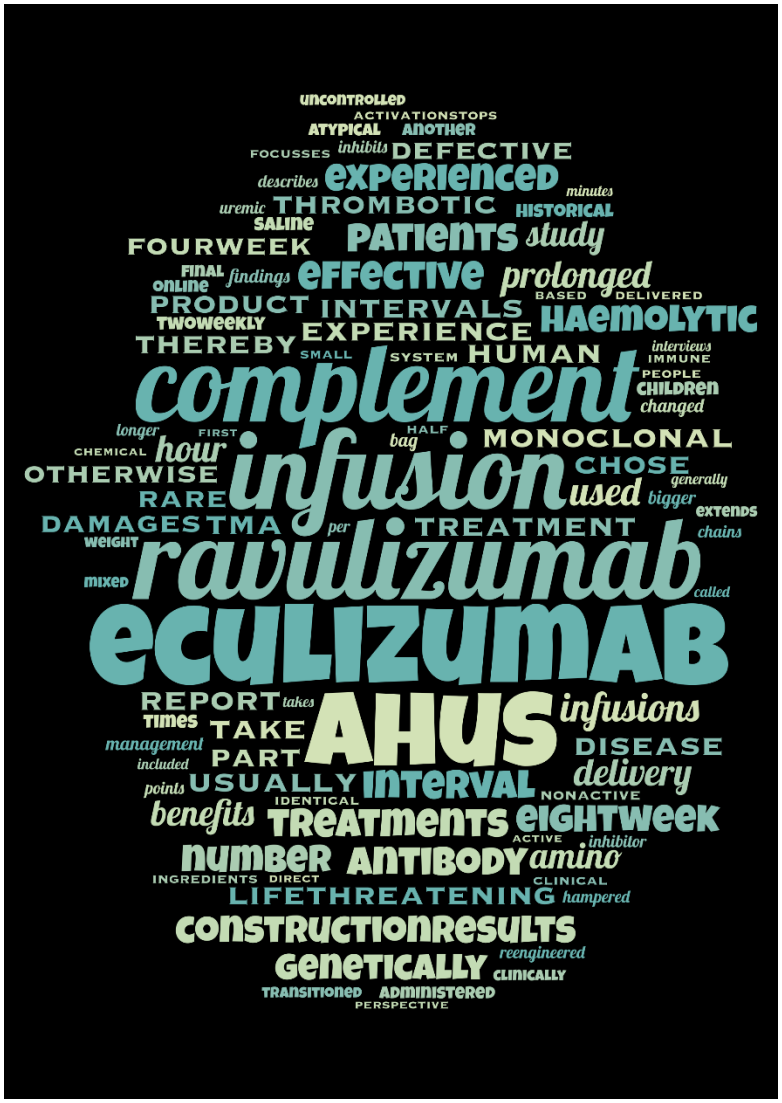

A REPORT ON THE COMPARATIVE EXPERIENCES OF THE IMPACT ON aHUS PATIENTS FOLLOWING A TRANSITION FROM ECULIZUMAB TO RAVULIZUMAB FOR THE TREATMENT OF aHUS

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1.Introduction

Atypical Haemolytic Uremic Syndrome, or aHUS, is an exceedingly rare life-threatening thrombotic microangiopathy, or TMA, which damages the kidneys in particular because of uncontrolled activation of a genetically defective or otherwise hampered part of the innate immune system called Complement.

Since 2011, when it was first licensed to be used, the most clinically effective treatment of aHUS has been a human monoclonal antibody called eculizumab. It inhibits unregulated Complement activation and stops TMA activity. It is delivered to patients by infusion of weight related doses, usually at two-weekly intervals. Infusion access is made via an implanted port, or direct into a vein or into a fistula for those patients who have been on haemodialysis (sometimes needled by patients themselves).

Another Complement inhibitor called ravulizumab has been developed by the same manufacturer. This too is a human monoclonal antibody identical to eculizumab but re-engineered with changes to four points in the amino acid chains of its chemical construction. The modifications result in a prolonged active half-life of the effective ingredient and therefore extends the interval between infusions. Maintenance dose infusions are usually administered at eight-week intervals for adults and a four-week interval for small children.

The non-active ingredients included in the final product are the same for both eculizumab and ravulizumab. Ravulizumab is however mixed into a bigger bag of saline for infusion than that used for eculizumab because of the higher number of vials of ravulizumab used per infusion. An infusion of ravulizumab can take more than three to five times longer than for eculizumab, which generally took 30 minutes to one hour.

This report describes the impacts experienced by aHUS patients who have transitioned from eculizumab to ravulizumab treatment.

The specific focus of the study is the delivery of both treatments rather than their clinical benefits compared with no treatment or a historical perspective on how disease management has changed over time. Participants weren't asked about other treatments which they may be receiving.

2. Methods Used

The research was conducted between 3 August 2020 and 12 September 2020.
There was no conflict of interest amongst any of the participants contributing to the study.

The method used was chosen because it was impractical to conduct extended, recorded face to face interviews in the time available. Interviewees felt comfortable with writing and talking about their experience.

The study report is therefore based on the results from 13 online interviews with people with direct experience of both treatments. No volunteers with experience of ravulizumab only participated in the study.

Participants volunteered to give statements following a social media call on 3rd August 2020 made via the aHUS alliance Global Action's website, Facebook Page and in a closed aHUS Families Facebook Group, for patients with experience of both eculizumab and ravulizumab use. Although the call for volunteers was to global aHUS patients, only patients from the USA offered to participate. The characteristics and time on both treatments of the participants are given in Table 1. The group's average time on eculizumab had been 4 years 5 months and 7 months on ravulizumab.

Table 1: Characteristics and treatment duration of experienced participants

Participant's Identifier	Participant's Role	Gender of patient	Age at August 2020	Time on eculizumab	Start month	Time on ravulizumab
A	Patient	Female	NK	NK	NK	NK
B*	Patient	Female	NK	4y 11m	5/20	4m
C	Patient	Female	46	9m	4/20	5m
D	Patient	Female	68	2y	1/20	8m
E	Patient	Female	51	6y 6m	12/19	9m
F	Carer	Male	11	10y 5m	2/20	7m
G*	Carer	Female	13	6y	11/19	10m
H	Patient	Female	47	6y	1/20	8m
I	Carer	Male	13	5y 6m	12/19	9m
J	Patient	Female	62	3y	1/20	8m
K	Patient	Female	38	3y	4/20	5m
L*	Patient/Carer	Male	23	1y 2m	5/20	4m
M	Patient	Male	22	4y 6m	12/19	9m

*transplant patient y -years m-months

The US Food and Drugs Agency (FDA) approved the use of ravulizumab on 18th October 2019 and so, by the time of this study, all experience of ravulizumab following transition is limited to less than a year, and to between 2 to 5 treatment cycles. No respondents had participated in any ravulizumab trial.

Participants provided some initial information when offering to volunteer, but all were written to with a further explanation of the purpose of the research, and what was expected of them, and to give assurance that information would be kept in confidence and participants anonymity would be maintained. Each was asked to write freely about what mattered to them in the transition, but some topic areas were suggested for them to think about. A follow up individual meeting by Zoom was offered and taken up by seven of the participants to clarify statements made and add further experience comments.

Each was asked about their length of time on both therapies. Details about their aHUS onset experience and recovery were not asked for but three volunteers mentioned that the patient had a kidney transplant.

The responses were pasted to a summary document for analysis. Themes were identified and comparable and contrasting views of participants summarised. This work was done by the Trustees of aHUS alliance Global Action.

3. Results: Impact statements from patients who have transitioned from eculizumab to ravulizumab treatment.

The results from the analysis of the responses are set out below. Quotes from interviewees appear *in italic* and are attributed to the role of the interviewee; patient or carer, as stated in Table 1.

A1. Transition process

The earliest transition from eculizumab to ravulizumab occurred within a month of FDA's approval of ravulizumab on 18 October 2019. Seven respondents said they had transitioned by the following January.

From those who disclosed it, the impetus to change mostly came from the patients themselves. They reported that they had been watching and waiting for FDA approval and had sought the move to ravulizumab when it became possible. For others it was their clinician who recommended a move. Several stated that their insurance providers were eager for them to change to ravulizumab treatment. Overall patients were keen to try it and generally were relaxed about doing so.

My doctor pushed for my switch to ravulizumab, but also my insurance company did as well, I'm assuming because it is less expensive. (Patient C)

With the FDA approval of Ravulizumab in October 2019, I requested the changeover immediately, but it was not cleared until January 2020 (Patient D)

Once the FDA approved ravulizumab, I contacted my doctor as well as the employer providing my insurance, because they started directly paying for my eculizumab treatment when their re-insurance denied coverage after a year. My doctor approved the change… (*Patient* E)

My son's doctor did first mention the medicine to us and started the process of insurance approval once it was FDA approved. It took about 3 months once the new medicine was FDA approved for both the hospital board to approve getting the medicine and insurance to preapprove the new medicine *(*Carer Patient F)

The transition was our choice. As soon as we heard of the FDA approval, I contacted our son's physician to begin the process. Our son was the first non-clinical trial paediatric patient in the US to transition (Carer Patient I)

I learned about the new drug being approved from a nurse in the infusion room…. so, I told the doctors I wanted to move to the new drug… insurance approved, and we moved (Patient J)

My doctors told me about ravulizumab so deciding to do it was nothing too crazy, whatever if it's better. (Patient L)

Once approved, the date for the transition protocol to be enacted was set. Two respondents reported some problems with meeting due dates but most reported that the move went to plan with no logistical issues. One mentioned the role played by their "case manager" in helping coordination.

My case manager was vital in coordination of many aspects between doctors, suppliers, facilities, and new nursing company (Patient E)

I started in April of 2020 I believe...then got off a week or so because of a pharmacy mistake (Patient K)

A2. Infusion Process

Two weeks after the last eculizumab infusion a loading dose of ravulizumab is administered. After a further two weeks the first maintenance dose begins and is followed up 8 weeks later and then so on. All respondents reported being on 8-week intervals between doses. No respondent commented on the volume of ravulizumab they were prescribed. On prompting at interview, two respondents reported that 10 and 11 vials of ravulizumab were prescribed according to their weight. (Note: compared with 16 vials of eculizumab for four treatment cycles over an eight-week period).

The increased length of the time taken over each infusion was mentioned because it was considerably more than for eculizumab, typically 2 to 5 hours, compared with 30 to 60 minutes reported for each eculizumab infusion. So, it is only marginally more than the aggregate time for four separate eculizumab infusions in eight weeks. Patients saw an advantageous quality of life trade-off between having longer infusions and a greater interval between infusions.

Participants reported that not having to attend for infusions every two weeks was a major benefit. Apart from the time gained to do other things, they mentioned how fewer infusions brought a physical and mental relief to the burden of treatment and made life easier for them.

One eculizumab home infusion patient reported a reversion to infusion centre practice for the first dose of ravulizumab so that any reaction could be monitored.

One carer mentioned that her son's access port has been removed to avoid unnecessary hospital visits for line flushing between infusions. Another carer of a patient with a transplant reported her daughter's port was retained for transplant monitoring procedures.

Another respondent reported that the loading dose of ravulizumab followed soon after an Ileostomy operation. The patient felt poorly at the time, with headaches and fatigue, but whether these were attributable to surgical recovery or ravulizumab was unclear.

…***Benefit from longer time in between infusion, thus giving my veins a res*t.** (Patient C)

My first treatment was delivered at my prior infusion facility to watch for reactions then returned to home infusion. (Patient E)

My son has been on eculizumab for all but 4 months of his life and is used to having infusions. Initially he was apprehensive about the extended infusion time but quickly adjusted when he realised it gave him more permitted time on his iPad. ***He had his port removed to avoid the need for flushing between 8-week infusions.*** (Carer Patient F)

I had a surgery to make my ileostomy permanent mid-December then transitioned to ravulizumab the first week of January. The recovery from surgery was more difficult than expected, but the team felt I should still transition in January. I felt poorly but I think that was from surgery more than the new med. I'd say the headaches and fatigue were worse. (Patient H)

The frequency of every 8 weeks has changed patients mental thinking. Going every 8 weeks, it is not so "in your face". (Carer Patient I)

While the infusion is longer, anywhere from 2-5 hours, having 8 weeks to live my life without thinking about the logistics of my next infusion is so freeing. (Patient M)

A3. Efficacy of the Technologies

Most respondents were confident that ravulizumab would be as effective for treating their aHUS as eculizumab had been.

My husband and I saw detailed data on the upcoming ravulizumab and were convinced it was as effective as eculizumab, particularly at keeping complement C5 shut down for the full 8 weeks in over 99% of cases (Patient E)

Several respondents mentioned that their blood results showed little difference following transition, with one respondent reporting a slight improvement after ravulizumab treatment. One patient, who transitioned, immediately following an operation, reported that the clinician had undertaken weekly blood tests in between infusions. Another respondent mentioned that the CH50 blood test was not available for ravulizumab treatment which raised her concern about monitoring efficacy.

The doctor says his labs look great so far and indications are good that the drug is doing well. (Carer Patient F)

My bloodwork has been monitored more closely than before… my clinician decided to take weekly bloods after the early infusions but phased them out over time…ravulizumab is proving to be just as stable as with eculizumab. (Patient H)

…there seems to be a lack of available blood testing to analyse complement blockade in ravulizumab, compared to CH50 with eculizumab. (Patient I)

***Since January, all my lab numbers remain intact*.** (Patient J)

Eculizumab cured all aHUS related health issues and ravulizumab does the same….my blood tests normalized after my initial diagnosis and have remained normal while I've been on eculizumab and ravulizumab. (Patient M)

A4. Side Effects

One respondent reported a side effect from ravulizumab so serious that a reversion to eculizumab was needed. Full details of the reason for the reaction were not provided. As this was the only comment made by the respondent it is not known whether this

was reaction to the re-engineered eculizumab, the change in infusion practice, or some breach of transition protocol affecting trough dose.

I went from long term eculizumab to ravulizumab ...had side effects on ravulizumab and I'm now back on eculizumab (Patient A)

Respondents' comments about other side effects were mixed. Some reported that they had no side effects with both eculizumab and ravulizumab; or the side effects were similar from each drug but limited to the infusion day or the day after. The most frequently cited side effects being a regular transitory headache and fatigue in the days following each infusion. Others mentioned included mild joint pain, sore throat, numbness in nasal/sinus area, pain at end of fingers/toes. Where asked, no patient regarded the side effects as debilitating. A small number of respondents felt their side effects were less after an infusion following ravulizumab transition. One respondent considered that the same side effects after treatment were stronger. Another who experienced a reaction to ravulizumab infusion found slowing down the rate of infusion improved matters. Although not leading to a reversion to eculizumab yet, one respondent felt that the bloating and an inability to lose weight while on ravulizumab is making her think about going back to eculizumab treatment.

***The side effects I experience seem to be a little stronger than with the eculizumab. They are, tiredness, (3-4 days after infusion) more intense joint pain, sore throat, and headache*.** (Patient C)

I had no reactions or side effects at any point on ravulizumab (or on eculizumab) (Patient E)

My son has had no obvious side effects with either medicine (Carer Patient F)

After my daughters first infusion she had an overall feeling of not feeling well, mostly body aches, so we decided to pre-treat with painkiller. That had helped and she really has had no other side effects (Carer Patient G)

I have not experienced any side effects that I didn't have with eculizumab. I think I have fewer headaches and less fatigue now than I did with the eculizumab. (Patient H)

I still have had no side effects from ravulizumab (Patient J)

*…**with my inability to lose weight and the bloating the ravulizumab is causing, I really don't know if I want to stay on it.*** (Patient K)

I feel tired and "not so good" on the day of the infusion and the next day and then I am ok again. (Patient L)

I have had a minor complication, and I never had issues with eculizumab. With ravulizumab the manufacturer recommends providers infuse over 2 hours. Unfortunately, for some reason, my body couldn't handle the drug at that rate, and I had a bit of a reaction the first time I used it. I've since slowed the infusion to 4 hours which I've been able to handle with no complications. (Patient M)

No respondent mentioned any concern about the major side effect from both drugs, i.e. the risk of a meningococcal infections. This perhaps indicates that they thought that any mitigating action taken for eculizumab would apply to ravulizumab too.

A5. Work, School, and Other Activities

Apart from a physical and mental relief from going through the infusion process less frequently, all respondents remaining on ravulizumab refer to the longer intervals as a key benefit, a "game changer". Respondents appreciated and made use of the new "freedom" it gave. The benefits are also felt by carers of patients.

…gives me more freedom because I don't have to worry about scheduling infusions as often… I would say that my day to day life has improved because of the longer time in between infusions. I am able to plan more activities, trips, etc. (Patient C)

Ravulizumab has certainly helped improve my lifestyle with having six versus twenty six infusions over a year period… my family live in Thailand and a two weekly infusion cycle, unless special carriage of properly stored eculizumab vials is arranged for away from home infusion, limits time I can spend there on visits. Ravulizumab improves my freedom to travel and stay longer*.* (Patient D)

The telling life story was that for the first time in 6 years, I didn't have to schedule an infusion during the holidays! Or arrange my vacation around it. (Patient E)

The time between infusions is a game changer as far as missed school for my son and missed work for myself*.* (Carer Patient F)

… as a nurse missing work as often as I did with eculizumab treatment caused me stress, that it might affect my salary status…ravulizumab has saved me a lot of lost work time, and less use of my precious PTO (paid time off) time … (Patient H)

Missing school once every other week was challenging (especially at higher grade level with multiple teachers). Infusion Center is 2 hours (100 miles) from home- 4 hours travel time, plus fuel and meals… we would also be able to spend more time at our holiday home on vacation as we will not need to return for infusion (Carer Patient I)

*…**with not having to plan my entire life around every other Wednesday for medicine is a huge advantage.*** (Patient J)

I wanted to switch for the convenience really. I work full time, plus my husband and I have 3 boys to raise (Patient K)

I would say he has more time for his favourite pastimes, walking and fishing as well as for his full-time job.... we even went on vacation last month to Arizona, 12 hours from here, that is something he would not have done on eculizumab, to go so far away from his home base and treatment (Carer Patient L)

Eculizumab ruled my life. I couldn't study abroad like the typical undergrad, since I needed to coordinate insurance, doctor's care, and eculizumab infusions every two weeks. My insurance company said they would cover two "grace" infusions abroad a year, but that would only allow me to spend a maximum of 6 weeks out of the country. The typical college study abroad program is 5-6 months. (Patient M)

A6. General health

No respondent mentioned the state of their, or their child's, general health but, when asked, they described it as "excellent" and transitioning to ravulizumab made no noticeable difference to that status.

… I feel so much better I have begun training to do a triathlon. (Patient H)

It is like my illness was a dream, unreal, because I feel so well on both drugs, like I was before it happened. (Patient J)

A7. Expense

A small number of respondents commented on the reduced cost of treatment they had observed, not just because of a lower price and fewer vials of ravulizumab needed at their weight, but from the savings also accrued due to less frequent infusion centre use and travel for treatment.

… and the health coverage provider told me it would save them 30% in overall costs. (Patient E)

Based on the figures I see from my insurance company; one other benefit is that it appears that ravulizumab infusions will cost much less on year than eculizumab did. (Patient J)

A8. Other Issues

One respondent reported that she had experienced a COVID 19 infection earlier in August 2020. The course of the disease, although typically symptomatic, ended quickly and she is now in quarantine working from home. There had been no problems from being on ravulizumab.

Other than this one respondent, the rest of participants mentioned no other issues other than topics summarised above.

In particular no one mentioned any change in their opinion about withdrawal from treatment. There was also no mention about treatment whilst pregnant.

A9. Overall Opinion

Most of the respondents reported that they were, on balance, satisfied with the transition from eculizumab to ravulizumab and preferring to be on ravulizumab. Ravulizumab makes life easier. Some considered that both were necessary.

I definitely prefer ravulizumab…. ravulizumab I feel is a step above eculizumab **(**Patient C)

You have to have both eculizumab and ravulizumab available as options. It seems like some patients do better on one or the other. Some have had to go back to eculizumab. (Patient E)

Overall, she has done really well with the switch and she has not regretted it**.** (Carer Patient G)

My experience with ravulizumab has been phenomenal…I'm extremely happy with ravulizumab, and very grateful I get to have it (Patient H)

I can breathe, I feel better not having so much treatment, it's simpler to do, making life easier. (Patient L)

Switching to the 8-week ravulizumab has been an incredible blessing (Patient M)

4. Conclusion

From those with experience of both technologies, the most telling benefit of ravulizumab over eculizumab is the substantial reduction in infusions needed which considerably increases the time between infusions.

The fewer treatments, reduces the cumulative pressure, anxieties and practicalities of each treatment over time , as well as releasing additional personal time to do other things, including those put off because of the insufficient inter-treatment gap e.g., long-distance travel for leisure or education.

Of importance too were the side effects of the new treatment. Most found little difference in post infusion transitory side effects, whether they had experienced any or none on eculizumab. Some perceived an improvement and two felt side effects had been sufficiently worse to revert, or think about reverting, to eculizumab.

With one exception, following transition participants had not observed any deterioration in the general health they attained whilst on eculizumab treatment. General health was usually claimed to be excellent.

With only minor logistical hiccoughs reported, the transition from one drug to another was not perceived as difficult to do, and so not a matter of importance.

Taken all together patients with experience of both therapies, see ravulizumab adding to their quality of life. Although it was not within the scope of this research to measure and quantify a value of the quality of life added, based on what has been voiced by participants it can be confidently predicted that it would be more than zero.

From the evidence provided by those with experience of both eculizumab and ravulizumab treatments patients see ravulizumab as a positive and progressive step change to their treatment. Although not perfect yet, it has much to commend it and is welcomed by aHUS patients.