

Rituximab to Abbreviate Plasma Exchange in Anti-CFH (Complement Factor H) Antibody Mediated Atypical HUS

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While terminal complement blockade with Eculizumab is the first line therapy for atypical HUS (Haemolytic uremic syndrome), lack of its availability and cost limits its use. Plasma exchange becomes a first line modality in the current scenario. However, exposure to large volumes of allogenic plasma and lack of skilled manpower are the limiting factors associated with it. Moreover, there is a subset of patients who fail to respond to plasma exchange.

Treatment and follow up records of the children with atypical HUS who did not respond to daily plasma exchange therapy and their course during follow up was reviewed.

Three children with positive anti-complement factor H antibody atypical HUS did not respond to daily plasma exchange and were administered Rituximab after completing five daily plasma exchange therapies. It was seen that these children, initially non-responsive to plasma therapy, attained remission after Rituximab and did not require further plasma exchanges. The remission was sustained in long term with a follow up of 7 years, 4 years and 6 months respectively. Rituximab might be a useful alternative in inducing haematological remission in children with poor or no response to plasma therapy. This abbreviates the duration of plasma exchange, which not only avoids complications due to prolonged plasma therapy but also helps reducing the cost of therapy.

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Atypical HUS is an ultra-rare disease and until recently it had a poor outcome. Anti-CFH antibody mediated HUS is considered a slightly milder version of illness as it's amenable to control using potent immunosuppressants such as Cyclophosphamide or Rituximab, which are now the standard therapies. There is an increased risk of progression to renal failure and a high risk of recurrence post-transplant.

Terminal complement inhibitor, Eculizumab is now the drug of choice for all forms of atypical HUS with additional immunosuppression required for antibody mediated forms of illness. However, the drug is expensive and not immediately available in many countries where plasma therapy (Plasma

exchange/plasma infusion) takes the first line. However, plasma exchange (PEX) becomes difficult due to lack of available skilled manpower and expenses. Moreover, there is a subset of patients who fail to respond to plasma exchange. We describe three children with antibody mediated atypical HUS who did not respond to initial therapy with plasma exchange. They were immunosuppressed with Rituximab (after no-response to plasma exchange), following which they attained remission and sustained it in long term.

We retrospectively retrieved and reviewed the treatment records of children treated at our centre with atypical HUS who had not responded to daily plasma exchange therapy and their follow up data

was collected.

There were three children with atypical HUS who had not responded to daily plasma exchange therapy. Each of their course is described briefly below (informed consent was obtained from all individual participants included in the study) (Table 1).

An 8-year-old boy presented with microangiopathic haemolytic anaemia and renal failure (as case 1). Atypical HUS was suspected, and plasmapheresis initiated after sending the samples for anti-factor H antibodies. [The assay was performed by ELISA technique, French method]. Plasma exchange was performed daily for 5 days initially. However, there was no haematological remission after initial daily exchanges. Immunosuppression was started with steroid and 2 doses of Rituximab were administered. Upon immunosuppression the child gradually responded as haemoglobin stabilised and platelet count improved. However, LDH persisted above upper limit of normal and renal dysfunction persisted over next 2 months during which the child remained dialysis dependent and on maintenance immunosuppression with steroid and Mycophenolate Mofetil (MMF). Two months later his renal dysfunction started to improve and he attained a creatinine of 0.9 and became dialysis free 4 months after disease onset. He is

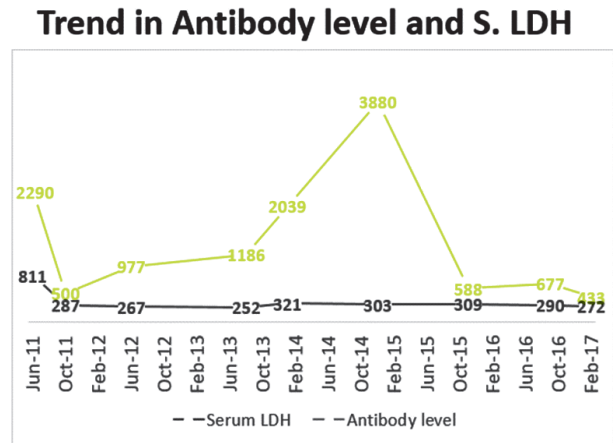
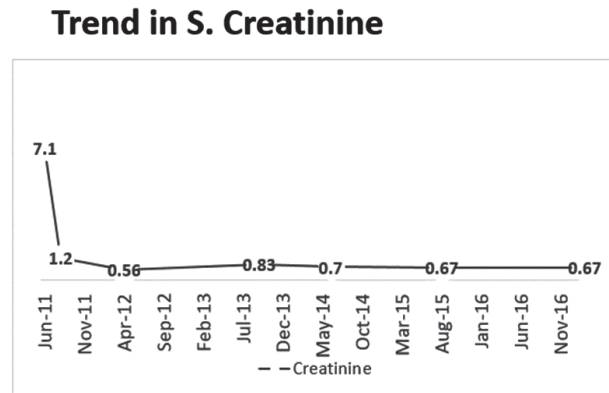
being followed up with bi annual antibody levels. A year after onset and then attaining remission he was noted to have a high titre of antibodies (> 2000 AU/mL) without any evidence of disease activity for which he received 2 more doses of Rituximab at another centre. He continued to have nephrotic range proteinuria for almost 1 year after disease onset which gradually resolved, and all immunosuppressions were withdrawn 3 years later. The child is now 16 years old with a 6-year relapse free follow up with normal renal function (creatinine: -0.7) and no proteinuria (Figure 1A). However he continues to be hypertensive requiring multiple antihypertensives for blood pressure control. Mutation studies could not be performed as they were not commercially available at the time this child was managed.

An eleven-year-old girl from Afghanistan presented with atypical HUS (as case 2). She had previously been admitted at another centre in Pakistan where she underwent 5 sessions of plasma exchange and there was no response to therapy. She was immunosuppressed with 2 pulses of Methyl Prednisolone followed by Rituximab, considering a high likelihood of antibody positive disease (Antibody level- 314 AU/mL). She started to respond and attained remission gradually over the next 3 months (Figure 1B). During her recovery

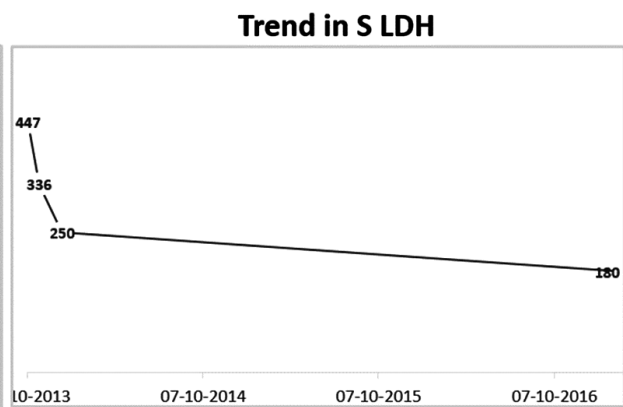
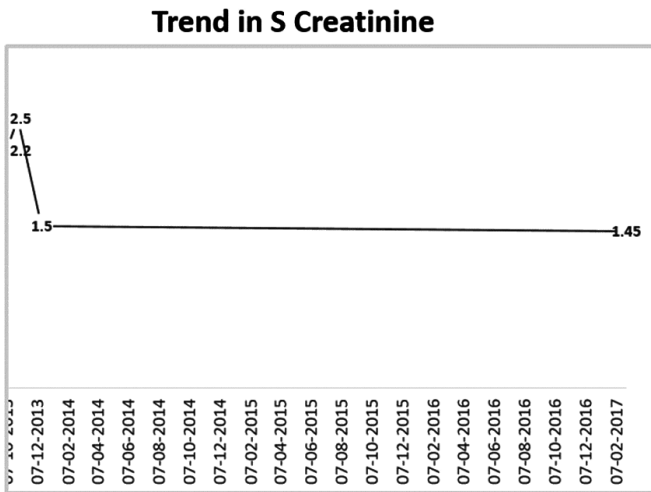
Table 1. The Profile of Each Patient

	Patient 1	Patient 2	Patient 3
Clinical Presentation			
Age/Sex	8 Y/M	11 Y/F	8 Y/F
Clinical Features	Anemia, Thrombocytopenia Renal Failure, Oliguria	Non Response to PEX Done at Another Centre, Persistent Renal Failure, Hypertensive Emergency and Microangiopathic Hemolytic Anemia	Microangiopathic Hemolytic Anemia, Post Blood Transfusion at Another Centre, Hypertension with PRES
Management			
Induction	5 PEX Daily, Rituximab: 2 Doses, Steroid, Anti- hypertensive (ARBs, CCBs)	5 PEX (Done at Another Centre), Methyl Prednisolone Pluse Followed by 2 Doses of Rituximab	5 PEX Daily, 2 Doses of Rituximab, Prednisolone (Relapse: 4 PEX, 2 Rituximab)
Maintenance	MMF + Steroid	MMF + Steroid	MMF + Steroid
Anti-CFH Antibody			
Antibody Titer Before Treatment	2290 AU/mL	314 AU/mL (Pre-plasma Pheresis Sample Was not Available)	13050 AU/mL
At Last Follow Up	433 AU/mL		2100 AU/mL
Outcome			
	Sustained Remission with Persistent Hypertension	Required admission subsequently for hypertension, then sustained remission	Relapsed 2 months later due to non-compliance, in sustained remission thereafter
Serum Creatinine at Last Follow Up	0.67 mg/dL	1.45 mg/dL	1.19 mg/dL

A) Lab Parameters Case 1



B) Lab Parameters in Case 2



C) Lab Parameters for Case 3

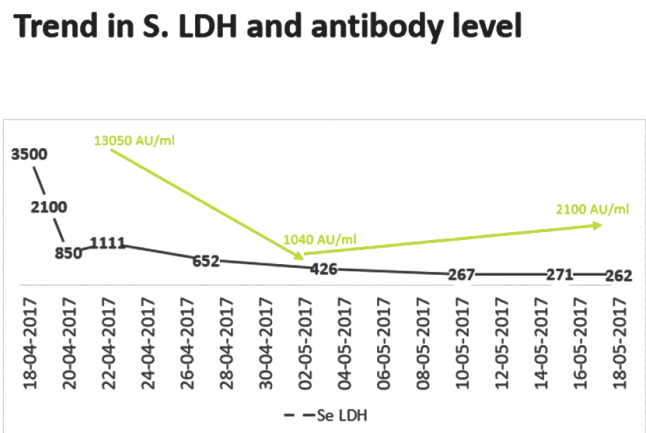
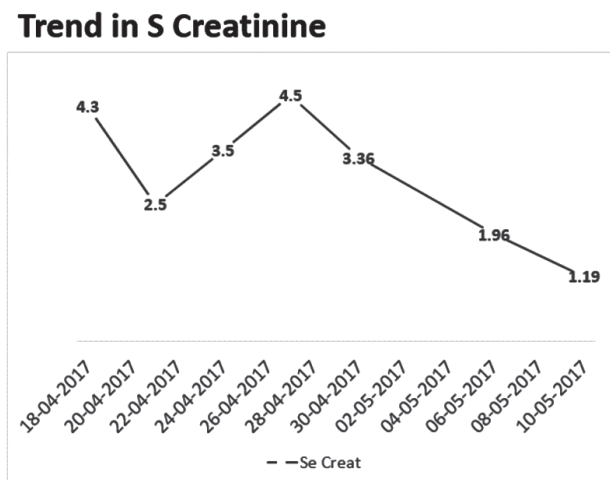


Figure 1. A, B and C, The graphs describe the trend in Serum creatinine after administration of Rituximab and depict the trend of serum LDH suggesting clinical and biochemical remission and antibody titres with time against the horizontal axis in each case.

she required multiple admissions for control of hypertension. During one of these admissions she even developed posterior reversible encephalopathy syndrome with seizures (PRES). She was later shifted to maintenance immunosuppression with mycophenolate mofetil (MMF) and prednisolone. Her last follow up after a relapse free survival of 4 years was in February 2017 when her creatinine was 1.45 with a urine protein creatinine ratio of .55. Mutation studies could not be performed.

The third child was an eight-year-old girl, who presented one month after the onset of illness with renal dysfunction anemia and thrombocytopenia, marginally improved after receiving blood transfusion at another centre prior to presentation here (as case 3). Daily plasma exchange was started for her during which she had no improvement in her hematological parameters and developed accelerated hypertension with seizures and PRES. Since the antibody for atypical HUS was positive (13050 AU/mL), immunosuppression was started with Rituximab, two doses were given 1 week apart, after completing 5 initial plasma exchanges. The child started to respond thereafter with gradual reduction in serum creatinine, increase in urine output and stabilisation of hematological parameters. She attained complete remission in next two weeks and sustained it further on maintenance immunosuppression with oral prednisolone and MMF for over a month. Her renal function improved and creatinine declined to 0.95 mg/dL. Despite this, she continued to have sustained hypertension and a month later developed features of relapse owing to poor compliance of medications. She underwent another cycle of plasma-exchange and received two more doses of Rituximab. She is currently in hematological remission but is still running high titres of antibody (2000AU/ML) (Figure 1C). Mutation studies were also performed in this child and none of the known mutations for atypical HUS were identified.

Atypical hemolytic uremic syndrome (a HUS) associated with anti-factor H antibodies (anti-CFH Abs) have been reported in 6% to 25% of patients in European cohorts.¹ In India up to 56% of the screened children are positive for antibodies.²

Plasma exchange is the preferred therapy specially where complement blockade is not available, as it reduces levels of antiCFH antibodies by removing them preferably performed daily till

hematological remission is attained.

The combined use of immunosuppressions is encouraged as it inhibits the production of antibodies and enables discontinuation of plasma exchange and/or treatment with eculizumab.³ There is currently no defined number of plasma exchanges that would be required to control the disease activity in each child, however most authors propose 5-7 daily plasma exchanges till hematological remission is attained followed by alternate day plasma exchanges and then tapering plasma exchanges with no clearly defined end point.^{3,4}

There is no clear benefit of tapering of plasma therapy versus abruptly discontinuing plasma therapy. However, maintenance immunosuppression is required in antibody mediated HUS with induction using steroid and cyclophosphamide or Rituximab and maintenance with tapering doses of steroid and Mycophenolate mofetil or Azathioprine.³

However, plasma exchange facility may not be always available at all places and is expensive. The risk of complications due to indwelling vascular access and use of blood products is always present. The complement blockade with Eculizumab is not available in many parts of the world and may be procured only through special order when it comes at an exorbitant cost that makes it practically unavailable for most patients at the time when it is needed the most i.e. within 24 hours of onset of illness. Though plasma therapy is effective, there is still no answer to the most effective therapy in the subgroup of patients who do not respond to plasma exchange despite daily therapy. It was recommended that one should switch to alternate therapy while there is no response after 5 days of daily therapy with either Eculizumab or plasma exchange.⁴ But what option do we have in a setting with cost constraints and non-availability of this holy grail. Role of Rituximab in children who do not respond/or respond late to plasma exchange has not been studied, though it is one of the recommended agents for induction of immunosuppression.^{5,7} Role of Rituximab in patients with anti-CFH antibodies is based on its depletion of B cells, leading, to reduced production of antibodies, and functional inhibition of CFH. The antibodies can be removed effectively by plasma exchange, and it has also been described that most reduction

with antibodies takes place with the initial daily plasma exchanges,⁸ therefore addition of rituximab to plasma exchange just after daily therapy might help in supporting use of abbreviated protocols of plasma exchange. Although it is likely that the disease remission is the result of depletion of antibodies by plasma exchanges, which may be apparent beyond the first week of exchanges, the cost incurred on the number of plasma exchanges may be brought down significantly.

The number of children we described is small and we need studies on a larger patient population for more robust data, and this was a major limitation of current report. Various reports in literature, mainly in adults have described that remission could be sustained in each patient only after rituximab was introduced.^{1,5}

We described through this paper the use of Rituximab in children who did not respond immediately to daily plasma exchanges and developed complications due to uncontrolled thrombotic microangiopathy. Since there are not many options to control disease activity in these children, we describe the use of Rituximab with steroid, as switch over therapy for those who do not respond /respond late to daily plasma exchanges while Eculizumab remains unavailable. These children attained remission after use of Rituximab and have been monitored for disease activity and relapses. Not only the children attained remission, but also did not require further plasma exchanges, hence the possibility of antibody getting removed by Plasma Exchanges was ruled out. This might be a helpful adjunctive approach to abbreviating the plasma therapy and overall helps reducing the cost of treatment.

The results presented in this paper have not been published previously as a whole or in part, except in abstract format.

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