

Plasma therapy in atypical haemolytic uremic syndrome: lessons from a family with a factor H mutation

Jean Claude Davin · Lisa Strain · Tim H. J. Goodship

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Abstract Whilst randomised control trials are undoubtedly the best way to demonstrate whether plasma exchange or infusion alone is the best first-line treatment for patients with atypical haemolytic uremic syndrome (aHUS), individual case reports can provide valuable information. To that effect, we have had the unique opportunity to follow over a 10-year period three sisters with aHUS associated with a factor H mutation (*CFH*). Two of the sisters are monozygotic twins. A similar natural evolution and response to treatment would be expected for the three patients, as they all presented with the same at-risk polymorphisms for *CFH* and *CD46* and no identifiable mutation in either *CD46* or *CFI*. Our report of different modalities of treatment of the initial episode and of three transplantations and relapses in the transplant in two of them, strongly suggest that intensive plasma exchange, both acutely and prophylactically, can maintain the long-term function of both native kidneys and allografts. In our experience, the success of plasma therapy is dependent on the use of plasma exchange as opposed to plasma infusion alone, the prolongation of daily plasma exchange after normalisation of haematological parameters followed by prophylactic plasma exchange, the use of prophylactic plasma exchange prior to transplantation and the use of prophylactic plasma exchange at least once a week

posttransplant with immediate intensification of treatment if there are any signs of recurrence.

Keywords Plasma exchange · Plasma infusion · Atypical HUS · FH mutation · Kidney transplantation

Introduction

In ~60% of patients with atypical haemolytic uremic syndrome (aHUS), mutations have been detected in complement components, including factor H (FH), membrane cofactor protein, factor I, factor B and C3 [1–5]. Factor H abnormalities are the most frequent, being found in ~30% of patients. The prognosis in this group is poor, with most patients developing end-stage renal failure (ESRF) and a recurrence rate posttransplant of ~80% [1, 6]. Although the use of plasma therapy is recommended, there is little consensus either with regard to efficacy or the optimal regimen to be used. To date, more than 100 FH mutations have been described (<http://www.fh-hus.org>). The penetrance of these mutations is ~50%, suggesting that other genetic and environmental factors act as modifiers [4]. Retrospective analysis of the response to plasma therapy in patients with FH mutations is supportive of a beneficial effect [2, 3]. To that effect, we have had a unique opportunity to follow over a 10-year period a family of three sisters with aHUS associated with a FH mutation (c.3572C>T, Ser1191Leu). The response to treatment has been of particular interest, as two of the sisters are monozygotic twins, and all three patients presented with the same at-risk polymorphisms for *CFH* and *CD46*. Therefore, they would be expected to present with a similar natural evolution of the disease and treatment response. Individual members of this family have been reported

J. C. Davin (✉)
Pediatric Nephrology,
Emma Children's Hospital/ Academic Medical Centre,
9 Meibergdreef,
1105 Amsterdam Z-O, The Netherlands
e-mail: J.C.Davin@amc.uva.nl

L. Strain · T. H. J. Goodship
Institute of Human Genetics, University of Newcastle Upon Tyne,
Newcastle Upon Tyne, UK

previously [7–10]. However, analysis of the whole family enables assessment of the effect of plasma therapy on the natural history of the disease in both native kidneys and allografts.

Case report

We summarise below our experience with plasma therapy in three sisters, two of whom are monozygotic twins, with atypical HUS associated with a FH mutation (c.3572C>T, Ser1191Leu) (Table 1).

In all three sisters, serum FH concentration has always been normal, and no evidence of systemic complement activation (such as a low C3) has ever been detected. Mutation screening of *CFI* and *CD46* revealed no abnormalities. Genotyping of the *CD46* single nucleotide

polymorphism (SNP) *4074T>C (rs7144) showed that all three sisters were heterozygous for the at-risk C allele. Genotyping of *CFH* SNPs showed that all three sisters were homozygous for the at-risk T allele of -332C>T (rs3753394), heterozygous for the at-risk G allele of c.2016A>G, Q672Q (rs3753396) and heterozygous for the at-risk T allele of c.2808G>T, E936D (rs1065489). Using multiplex ligation-dependent probe amplification (MLPA), all three sisters were found to have two copies of *CFHR1* and *CFHR3*.

The other family members (father, mother, an older brother and an older sister) were asymptomatic. The disease manifested first in the older sister when she was 3 years old and resulted immediately in ESRF. Her first renal transplant at the age of 5 years was lost to recurrent HUS within weeks of surgery. Plasma therapy was not given at that time.

Table 1 Clinical history of a family of three sisters presenting with factor H (FH) mutation-related haemolytic uremic syndrome (HUS)

Patients	Older sister	Twin 1	Twin 2
<i>Native kidneys</i>			
Age (years) at presentation	3	4	4.5
PE (40 ml/kg/session)	No	10 daily sessions initially	21 daily sessions initially
PI Cr ($\mu\text{mol/l}$) response to initial PE		166→137	132→61
PI (10 ml/kg)	No	3 courses of 5 PI	No
Prophylactic PE 1×2w	No	No	Yes
Relapses	Immediate ESRF	3 relapses of haemolysis and thrombopenia	2 after 3 and 19 months, respectively
Outcome	Immediate ESRF	Progressive degradation of renal function. ESRF after 4 months	PI Cr 66 $\mu\text{mol/l}$ after 6 years, no urinary abnormality
<i>Tx 1</i>			
	Cadaver	Cadaver	No
Prophylactic PE 1/w	No plasma therapy	Yes after initially prior Tx and daily during 7 days post-Tx	
Immunosuppressive therapy	ATG, Pred, AZA, CsA	Pred, MMF, CsA (low doses), Basiliximab	
Relapses	2 days after Tx no plasma therapy	2 relapses concomitant to CMV primo-infection and reactivation; successful treatment with daily PE and ganciclovir	
Outcome	Transplantectomy	P2 Cr 127 $\mu\text{mol/l}$ 5 y after Tx	
<i>Tx2</i>			
	Cadaver	No	No
Prophylactic PE 1/w	During the first 2 month, after initially prior Tx and daily during 7 days post-Tx		
Prophylactic PE 1/2w	Initiated 2 months post-Tx		
Immunosuppressive therapy	Pred, MMF, CsA(low dosis), Basiliximab		
Relapse	Occurred when PE frequency shift to 1/2w;		
Outcome	Immediate post-Tx function (PI Cr 80 $\mu\text{mol/l}$ 1 until day 60). Transplantectomy at day 75 related to late initiation of daily PE		

PE plasma exchanges, PI plasma infusions, ESRF end-stage renal failure, PI Cr plasma creatinine, Tx kidney transplantation, CMV cytomegalovirus, Pred prednisone, MMF mycophenolate mofetil, CsA cyclosporin A, Aza azathioprine, ATG anti-thymocyte globulin

One year later, one of the twins (twin 1) presented with the features of HUS. Plasma exchange (PE) was initiated, and ten daily sessions of PE (40 ml/kg per session) undertaken. Platelet count normalised, the evidence of haemolysis resolved but plasma creatinine decreased only slightly from 166 to 137 $\mu\text{mol/l}$. She received thereafter three sessions of five plasma infusions (10 ml/kg) in response to recurrent thrombocytopenia and haemolysis with good effect. However, plasma creatinine continued to increase, and ESRF was reached 4 months after presentation.

Six months later, her twin sister (twin 2) presented with the disease. Because of the dramatic evolution of the two other sisters and the good response to plasma therapy in twin 1, an intensified plasma therapy protocol was implemented. Daily PE was performed until normalisation of plasma creatinine after 3 weeks (132 $\mu\text{mol/l}$ to 61 $\mu\text{mol/l}$). Thereafter, PE was undertaken once every 2 weeks. Three and 19 months later, thrombocytopenia and haemolysis in association with a respiratory tract infection prompted a temporary increase in the frequency of PE to daily. Following the second relapse, weekly PE was undertaken for 6 months, followed by a frequency of once every 2 weeks indefinitely. There were no further relapses, and renal function was normal six years after presentation.

This response to intensive PE prompted us to undertake transplantation with prophylactic plasma therapy in her two sisters. The older sister was transplanted for the second time at the age of 12 years with a cadaver kidney. Immunosuppression comprised prednisone, cyclosporine (maximum trough level 150 $\mu\text{g/ml}$), anti-interleukin-2-receptor (IL-2-R) antibodies and mycophenolate mofetil. PE was undertaken immediately prior to transplantation, daily for the first postoperative week, and then progressively tapered to once every 2 weeks by 2 months posttransplant. The graft functioned well (plasma creatinine 80 $\mu\text{mol/l}$) until 2 months posttransplant, when plasma creatinine increased to 200 $\mu\text{mol/l}$, without either evidence of thrombocytopenia or significant haemolysis. A clinical diagnosis of acute rejection was made, and treatment commenced with pulse methylprednisolone. A renal biopsy performed 5 days later following a further deterioration in transplant function showed HUS, and despite an increase in the frequency of PE, the graft did not recover.

Twin 1 was the second to be transplanted, also with a cadaver kidney. We used an identical immunosuppressive regimen. PE was undertaken as in her older sister, but the frequency of PE was never decreased to less than once a week. There was immediate graft function, and plasma creatinine fell to 80 $\mu\text{mol/l}$ within days. Ten months posttransplant, she presented with biopsy-proven recurrent HUS associated with primary cytomegalovirus (CMV) infection. The plasma creatinine was 167 $\mu\text{mol/l}$. After 4 weeks treatment with daily PE and ganciclovir, plasma

creatinine stabilised at 90 $\mu\text{mol/l}$. When ganciclovir was stopped 6 months later, there was a further episode of recurrent HUS, and plasma creatinine increased to 187 $\mu\text{mol/l}$. Again, intensification of PE and the use of ganciclovir resulted in recovery of graft function. Continuous CMV prophylaxis with acyclovir was instituted, and no further episodes of either CMV reactivation or recurrent HUS were seen. Five years after transplantation, plasma creatinine was 127 $\mu\text{mol/l}$, and transplant biopsy showed allograft nephropathy but no HUS activity.

PE was performed using plasma filtration technique with a Gambro filter PF 1000 N and a Gambro device AK 200. Reactions to plasma were rarely observed and were always reversible using steroids and antihistaminic treatment.

Discussion

None of the affected members of this family showed evidence of systemic complement activation. This is in keeping with functional studies that show that mutations in the C-terminal domains of FH lead to reduced binding to surface-bound C3b and heparin, whereas the capacity to bind fluid-phase C3b is maintained [11]. The FH mutation (S1191L) found in the three affected sibs in this family has been reported previously in another HUS patient [12]. Although the functional significance of this mutation has not been examined, other missense mutations (W1183L, V1197A, R1210C, R1215G) in the same complement-control protein module (CCP 20) of FH have been shown to result in impaired protection of host surfaces against complement activation [11, 13]. It has been recently shown that multiple additive factors, including both mutations and susceptibility factors, in other complement genes are probably responsible for the $\times 50\%$ penetrance seen in aHUS [4]. In these three patients, no mutations in either *CD46* or *CFI* were detected, and there was no evidence of deletion of either *CFHR1* or *CFHR3*, as previously described in association with aHUS [14]. However, all three presented with the same at-risk polymorphisms of *CFH* and *CD46*.

The efficacy of plasma therapy is difficult to assess in recent large series, because treatment modalities are poorly described [2, 3]. The general impression is that plasma therapy is beneficial in patients known to have either a *CFH* or *CFI* mutation, whereas it does not appear to influence the outcome in patients with an *MCP* mutation [2, 3].

It is possible that the improvement seen in twin 2 after her initial presentation was not related to PE, as spontaneous recovery has been reported previously [2]. This is unlikely because of the severity of the disease in her two sisters and the similar profile of *CFH* and *CD46* susceptibility factors in the three patients. Our observation confirms previous

reports on the role of plasma therapy in aHUS associated with FH deficiency [2, 3, 15–18]. It confirms also that plasma infusions do not always prevent deterioration of renal function or relapses, even when given prophylactically [18]. A possible cause of the failure of plasma infusion treatment reported in the latter study as well in twin 1 in this study may be that the volume of plasma allowed by infusion alone (10 ml/kg) is four times less than the amount used in PE. Another possible cause may be the type of mutation and the resulting functional defect. In the report of Nathanson and coworkers, a child with total FH deficiency due to a homozygous *CFH* mutation was successfully treated with plasma infusions [17]. In this patient, 13.5 ml/kg of fresh frozen plasma infused every 2 weeks was associated with a relapse-free period of several years. A similar successful short-term outcome was seen in another patient with complete FH deficiency by using plasma infusions (20 ml/kg) both during relapses and prophylactically [16]. The duration of the daily PE treatment may also be important, as the initial episode in twin 1 was treated daily for 10 days compared with 3 weeks for twin 2. The degree of renal failure at presentation does not seem to explain the different responses to PE, as the difference between plasma creatinine at treatment initiation in both twins was minimal (166 vs. 132 $\mu\text{mol/l}$).

The risk of recurrence of aHUS in allografts is at least 20% [1] and is higher in patients known to have an FH mutation [1]. The risk of early graft loss after recurrence in some series of familial HUS is close to 100% despite treatment [19]. For this reason, it has been suggested by some that transplantation is contraindicated in familial HUS [20]. A particularly high risk of relapse was observed in this family, as the illness recurred in the three transplants performed in two patients. However, PE profoundly influenced the natural history of the disease both in native kidney and transplants. The first transplant in the oldest sister was performed without prophylactic PE and was associated with immediate relapse and transplant loss. In the same patient, the second transplant performed with prophylactic PE had good function until 2 months post-transplant. At that time, PE frequency was reduced to once every 2 weeks, and at that time, there was a deterioration in transplant function. This was initially felt to be secondary to rejection and intensification of PE was delayed. Subsequently, the graft was lost. The third transplant, performed in twin 1 under PE prophylaxis, resulted in satisfactory long-term function (plasma creatinine 127 $\mu\text{mol/l}$ after 5 years) despite several relapses associated with CMV infection.

In conclusion, in this family with atypical HUS associated with a FH mutation, we have shown that intensive and prophylactic PE has enabled maintenance of native and transplant renal function. The success of plasma therapy was associated with the use of PE and not plasma

infusion, prolongation of daily PE after normalization of haemolysis followed by prophylactic PE, the use of prophylactic PE prior to transplantation and the use of a minimum long-term PE frequency of once a week and immediate intensification of PE frequency in case of relapse.

As mutations of FH are heterogeneous, our strategy of intensive and prophylactic PE may not be necessary in all patients with FH mutations. Indeed, several authors have reported success with plasma infusions [16, 17]. The strategy of prophylactic PE is expensive, necessitates creation of an arteriovenous fistula and implies life-long regular treatment in hospital. It is likely that purified FH will become available within the next few years, and this may provide sufficient FH in a small volume to replace PE. However, PE is not only a means to provide high volumes of plasma but also removes mutant FH. Recently, success has been obtained by combined kidney–liver transplantation with prophylactic PE immediately prior to transplantation [21]. Treatment choice should take into account the benefit versus risk as well as the local feasibility and financial aspects.

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