Plasmatherapy in Atypical Hemolytic Uremic Syndrome

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ABSTRACT

Plasmatherapy has become empirically first-line treatment in atypical hemolytic uremic syndrome (aHUS), although no prospective controlled trials have been conducted. Patients with mutations that induce complete or partial factor H (FH) quantitative deficiency may be controlled by plasma infusions (PI), but plasma exchanges appear more efficient than PI in patients with mutations that result in a mutant dysfunctional FH in the circulation. Early treatment is crucial. Long-term prophylactic plasmatherapy appears more efficient to prevent end-stage renal disease (ESRD) than plasmatherapy only during relapses. However, the longest follow-up with preserved renal function under plasmatherapy is only 6.5 years. Plasmatherapy does not appear to influence the outcome of aHUS with membrane cofactor protein mutation, and its efficacy in patients with factor I, C3, or factor B mutations is suggested by a few reports. We hope complement blockers will offer patients a better chance to avoid ESRD and provide a better quality of life.

KEYWORDS: Atypical hemolytic uremic syndrome, plasma infusions, plasma exchange, complement

Over the last decade, atypical hemolytic uremic syndrome (aHUS) has been demonstrated to be a disorder of the complement alternative pathway regulation.[1] Four alternative pathway regulatory proteins—factor H (FH), membrane cofactor protein (MCP or CD46), factor I (FI), and thrombomodulin (THBD)—and two proteins of the C3 convertase—factor B (FB) and C3—are now implicated. The overall mortality in the acute phase is ~10%, and evolution to end-stage renal disease (ESRD) occurs in 50% of patients.[1–4]

Plasmatherapy was first considered for HUS patients 30 years ago when its benefit was demonstrated in thrombotic thrombocytopenic purpura (TTP).[5–8] However, until the 1990s, the distinction between HUS due to Shiga-toxin-producing *Escherichia coli* (STEC-HUS) and aHUS, or between aHUS due to complement dysregulation and TTP due to hereditary or immune ADAMTS-13 deficiency was not established. Therefore, the only two prospective randomized trials ever performed in HUS, nearly 25 years ago, which showed no clear benefit from plasma infusions (PI) in children with HUS.[9,10] cannot be regarded as arguments against plasmatherapy in aHUS because they did not differentiate patients with STEC-HUS (probably the majority, now known as nonresponsive to plasmatherapy) from those with aHUS or TTP.[11,12] When these differentiations were clarified, plasmatherapy empirically became first-line treatment in aHUS.[13,14]

Here we review the published data and recommendations for plasmatherapy in aHUS according to

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genotype. Plasmatherapy in anti-FH antibodies aHUS and post-transplant aHUS recurrence is developed in other articles of this issue of *Seminars in Thrombosis and Hemostasis*.

THE RATIONALE OF PLASMATHERAPY IN ATYPICAL HEMOLYTIC UREMIC SYNDROME

Plasmatherapy consists of either infusion of fresh-frozen plasma (FFP) or plasma exchange (PE) with volume restitution by FFP. Viro-inactivated/pathogen-reduced FFP produces normal amounts of complement factors FH, FI, FB, and C3. FFP does not contain MCP and THBD, two noncirculating transmembrane proteins.

First, PE allows delivery of high quantities of FFP (generally 40 to 60 mL/kg per session), and thus of nonmutated factors, without the risk of volume overload, hypertension and cardiac failure, and hyperproteinemia, a complication with possible deleterious hemorheologic and renal consequences, when PI (10 to 20 mL/kg per infusion) are repeated two to three times weekly.[15,16] Second, it also allows removal of mutated factors. Theoretically, this may be important when the mutation results in a dysfunctional protein. Most mutations of *CFH* and all those in *CFI, CFB,* and *C3* reported in aHUS are heterozygous, suggesting a dominant negative effect of the mutant protein on the normal protein. Third, PE could also be of benefit by removing other triggers (e.g., cytokines) of endothelial dysfunction and platelet hyperaggregability.

The analysis of the effect of plasmatherapy in retrospective case series is difficult because of varying parameters (e.g., delay between onset of HUS and initiation of treatment; plasmatherapy modalities [PI or PE; if PE, restitution with either albumin or FFP]; volume of FFP infused or exchanged; frequency and duration are not homogeneous). No prospective randomized controlled trials to prove the efficacy of plasmatherapy have been conducted in aHUS. Therefore, although most patients received some form of plasmatherapy, only a limited number of case reports are available to answer the question of the benefit of plasmatherapy in aHUS.

Plasma sensitivity is generally defined by the increase of platelet count and cessation of hemolysis (stabilized hemoglobin, normalization of lactate dehydrogenase [LDH] ,and haptoglobin levels). Plasmatherapy may fail to rescue renal function despite hematologic remission if treatment initiation has been delayed and/or histological lesions are irreversible. Therefore, the response to plasmatherapy may be complete (hematologic and renal remission) or partial (hematologic remission with renal sequelae).

PLASMATHERAPY IN PATIENTS WITH *CFH* MUTATIONS

Prognosis of aHUS associated with *CFH* mutations is the most severe, with evolution to death (20 to 30% of patients) or ESRD (40% of survivors) at first episode or during the year of onset in 60 to 70% of patients.[1–4]

Retrospective Series

The main retrospective series was published in 2006 by Caprioli et al.[2] Most aHUS episodes (57 of 61 episodes in 47 patients) were treated by plasmatherapy, consisting of PI 10 to 20 mL/kg and/or PE 30 to 40 mL/kg, for a total of 2 to 36 treatments in 2 to 6 weeks. A complete or partial remission was observed in 38 of 57 treated episodes (67%) and 4 of 4 untreated. However, 30% of patients died, 22% went on to ESRD, 30% had renal sequelae, and only 17.5% had complete remission at first episode; 78% had died or developed ESRD at long-term follow-up.

Case Reports

CFH mutations are classified here as type 1 if they induce a FH quantitative deficiency (low FH plasma level) or type 2 if they result in a dysfunctional FH (normal FH plasma level), according to Saunders et al.[17]

COMPLETE FACTOR H QUANTITATIVE DEFICIENCY (HOMOZYGOUS OR COMPOUND HETEROZYGOUS TYPE 1 MUTATIONS)

The first patient with complete FH deficiency and two episodes of HUS rescued by PE was reported in 1994.[18] Subsequently, a large consanguineous Bedouin family was reported. Eleven siblings had aHUS, a homozygous type 1 mutation and complete FH deficiency.[19] All had neonatal onset and a relapsing course. The first 10 siblings were treated with PI, daily during acute episodes, weekly between episodes. Eight died of complications of HUS and two went on to ESRD in early life. The sibling reported in 2001 by Landau et al,[20] who was initially treated as per his siblings, had a mean of two relapses per month under PI 10 mL/kg weekly, which dropped to one relapse over 9 months when the volume of PI was increased to 15 to 20 mL/kg twice weekly. Serum creatinine was 40 μmol/L at 17 months follow-up.

The effect of plasmatherapy has been reported in a total of five patients with complete FH deficiency[3,20–24] (Table 1, patients 12 to 16). Two were treated at the first episode by PI. Spontaneous remission occurred in the three others. Preventive plasmatherapy was instituted in four patients, with PI 10–20 mL/kg from twice weekly to every 2 weeks; one child (patient 16) was treated only during relapses. Plasmatherapy rescued renal function not only in patients with mild renal insufficiency (patients 13,

Table 1 Plasmatherapy Modalities and Effect in Patients with Complete Factor H Deficiency

Patient	Author	Age at Onset	Genotype	Screat μm/L*	Plasmatherapyat First Episode	Long-Term Plasmatherapy	Outcome (follow-up)
1	Pichette et al[18]	19 yr	ND, FH < 5%	1574	PE (1 L) × 21 over 6 wk	No. relapse after 4 mo →50 PE→dialysis-independent after 9 mo	Screat 195 μm/L (6 yr)
2–11	Ohali et al[19]	1–10 wk	HO 3749del24bp SCR20	/	PI 10 mL/kg daily	PI 10 mL/kg weekly between relapses, daily during relapses (3.9 relapses/P)	Death: 8 (age 1–10 mo) Dialysis: 2 (age ≤1 yr)
12	Landau et al[20]	10 d	HO 3749del24bp SCR20	274	PI 10 mL/kg daily	PI 10 mL/kg weekly × 8 mo (16 relapses), then 15–20 mL/kg twice weekly × 9 mo (1 relapse)	Preserved renal function (17 mo)
13	Nathanson et al[21,22]	5 mo	HO Y899X, SCR15	128	/	PI 13–15 mL/kg weekly from age 4 to 8 yr	Plasma resistance (PE 60 mL/kg × 11 d) and ESRD (4 yr)
14	Licht et al[23]	8 mo	HO Y899X, SCR15	97	/	PI 20 mL/kg every 2 wk × 18 mo	Preserved renal function (18 mo)
15	Sellier-Leclerc et al[3]	6 mo	HO 3768–71delAGAA SCR20	465	PI 10 mL/kg × 12 d tapered to weekly after 3 mo	PI 10 mL/kg weekly × 2 yr	Preserved renal function (2 yr)
16	Cho et al[24]	22 d	Compound HE, C1077W,SCR18 Q1139X, SCR19	106	/	No. each relapse treated by PI 15 mL/kg × 3/wk, tapered over 3 mo	Relapses at 2 mo, 9 mo, 18 mo, 19 mo. Preserved renal function (19 mo)

*At initiation of plasmatherapy.
ND, not documented; PE, plasma exchange; Screat, serum creatinine; to convert from μm/L to mg/mL, × 0.0113; HO, homozygous; PI, plasma infusion; P, patient; HE, heterozygous; ESRD, end-stage renal disease.
P13 and 15 were reported as P1 and 3, respectively, in Sellier-Leclerc et al.[3]

14, and 16) but also in the two with severe renal involvement (patients 12 and 15). Over the long term, all five patients had preserved renal function after 17 months to 4 years on plasmatherapy. By contrast, an untreated child with the same homozygous *CFH* mutation as patient 15 went on to ESRD within 3 months.[25] However, in the child with the longest follow-up (patient 13), a relapse after 4 years on plasmatherapy could not be rescued by daily PE. This secondary plasma resistance was not due to anti-CFH antibodies.[22] This patient later presented sudden unilateral blindness after 3 years of dialysis without plasmatherapy, with ischemic/hemorrhagic retinal lesions. Daily PE (60 mL/kg) during 10 days, then three per week, allowed recovery of vision after 4 weeks.[26]

Landau et al[20] were the first to show that 20 mL/kg PI increased FH serum level from near zero to ~25% of normal, with a progressive decrease to 10% after 72 hours. This was confirmed by Licht et al,[23] who showed that the estimated half-life of FH was ~6 days, and that the low C3, AP50, and CH50 levels reflecting complement activation increased after PI and declined progressively thereafter. Thus it appears that in patients with type 1 *CFH* mutations, who have a quantitative deficiency of FH but no mutant FH in circulation, increasing FH concentration from zero to 25% of normal, and maintaining this level continuously thereafter, may suffice to prevent episodes of HUS. However, the longest published follow-up is only 4 years.[22]

PARTIAL FACTOR H QUANTITATIVE DEFICIENCY (HETEROZYGOUS TYPE 1 MUTATIONS)

The effect of plasmatherapy is documented in only two patients who probably enter this category because they had FH levels ~50% of normal. However no *CFH* mutation could be identified[27,28] (Table 2A, patients 1 and 2). One of them needed 4 months of PE/PI before dialysis withdrawal was possible (patient 1). The other was maintained on weekly plasmatherapy and had moderate renal insufficiency at 3 years follow-up (patient 2).

MUTANT DYSFUNCTIONAL FACTOR H (HETEROZYGOUS TYPE 2 MUTATIONS)

Although heterozygous type 2 mutations are the most frequent, the effect of plasmatherapy is documented in only six children[16,29–32] (Table 2B, patients 1 to 6). All had mutations in FH SCR 19 or 20, the hot spots for FH binding to C3b and polyanionic sites at cell surface, and five had the same S1191L mutation in SCR20.[33] In four patients (patients 2, 3, 4, and 6), the initial episode was rescued by PE, two of them after PI had failed to control the disease. Starting plasmatherapy before renal function is severely impaired probably is important: The four children with a positive response had mild/moderate renal failure at treatment initiation (patients 2, 3, 4, and 6; serum creatinine 132 to 166 μmol/L), whereas patient 5, who had PE started 4 weeks after onset, when serum creatinine was 442 μmol/L, did not recover renal function. Subsequently, two children received plasmatherapy only during relapses. Both were in ESRD 4 and 2.5 months after onset, respectively (patients 2 and 5). In contrast, the four patients (patients 1, 3, 4, and 6) who received preventive plasmatherapy, 40 mL/kg FFP infused or exchanged from weekly to every 2 to 3 weeks, all had preserved renal function after 1.5 to 6.5 years under plasmatherapy. However, the child with the longest follow-up developed progressive renal failure after 6.5 years of treatment and reached ESRD within 1 year.

The family reported by Davin et al[29] suggests that long-term PE therapy may have benefits over PI alone. In these monozygotic twin sisters with S1191L mutation (Table 2B, patients 2 and 3), the first episode of HUS was rescued by PE. Subsequently, the first twin (patient 2) had three relapses within 4 months, each treated by 5 PI, 10 mL/kg. She developed ESRD 4 months after onset. Therefore, the second twin (patient 3) was maintained on a program of prophylactic PE, 40 mL/kg every 2 weeks. After 6 years follow-up, her serum creatinine was 49 μmol/L.[29]

Of note, all these patients had relapses of HUS despite plasmatherapy, mostly during upper respiratory tract infections, rescued by intensification of treatment at the very first symptom of relapse, generally a slight decrease of platelet count.

In conclusion, although published data on plasmatherapy in *CFH*-HUS is limited, these suggest that (1) early initiation of plasmatherapy is crucial; (2) PE is more effective than PI for remission and prevention of relapses, at least in patients with type 2 *CFH* mutations; (3) patients maintained on preventive plasmatherapy have a more favorable outcome than patients treated only at the time of relapses; (4) the schedule for long-term preventive plasmatherapy has to be determined empirically for each individual patient, to define the modality (PE or PI), threshold volume, and frequency necessary to maintain remission; (5) too rapid tapering or withdrawal of plasmatherapy generates a risk of relapse and ESRD; (6) plasmatherapy, or at least biological controls, must be intensified during infectious/inflammatory (e.g., vaccinations) triggers of relapses; (7) it is uncertain whether preserved renal function can be maintained for more than a few years by plasmatherapy.

FH concentrate or recombinant FH logically ought to have therapeutic value in patients with type 1 mutations who only need FH repletion. Whether these products will be sufficient in patients with type 2 mutations, for instance during remission for the prevention of relapses, will have to be established.

Table 2 Plasmatherapy Modalities and Effect in Patients with Partial Factor H Quantitative Deficiency or Dysfunctional Factor H

Patient	Author	Age at Onset	Genotype	Screat μm/L*	Plasmatherapy at First Episode	Long-Term Plasmatherapy	Outcome (follow-up)
A. Partial FH quantitative deficiency							
1	Stratton and Warwicker[27]	33 yr	ND. Low FH	1066	PE 40 mL/kg × 1 wk; then weekly × 3 mo; then PI 15 mL/kg × 1 mo	No	Dialysis- free after 120 d Screat 212 μm/L (1 yr)
2	Gerber et al[28]	3 mo	ND. Low FH, no anti-FH antibodies	132	No; 3 relapses over 4 mo	PE weekly from age 7 to 11 mo; then PI 20 ml/kg weekly × 2 yr 8 mo, intensified to twice weekly during 4 relapses	GFR 50 mL/min/1.73 m^2 (3 yr)
B) FH dysfunction							
1	Filler et al[16]	1 yr	HE Insertion of 12 amino acids, SCR20	85	No; 4 relapses over 2.5 mo	PI 30 mL/kg twice weekly or 40–45 mL/kg weekly, or PE 40–45 mL/kg weekly or every 4–5 wk with PI in between × 1.5 yr	Screat 35 μm/L (1.5 yr)
2 1st twin	Davin et al[29]	4 yr	HE S1191L, SCR20	166	PE 40 mL/kg × 10 d	No. PI 10 mL/kg × 5 during 3 relapses	ESRD (4 mo)
3 2nd twin	Davin et al[29]	4.5 yr	HE S1191L, SCR20	132	PE 40 mL/kg × 21 d	PE 40 mL/kg every 2 wk × 6 yr intensified to weekly during 2 relapses	Screat 62 μm/L (6 yr)
4	Lapeyraque et al[30]	7 mo	HE S1191L, SCR20 V1197A, SCR20	166	PI 14 mL/kg × 3 d; then 40 mL/kg × 8→ failure; PE 40 mL/kg × 4 d then twice weekly →remission	PE twice weekly (daily if infection) × 1 year then PI 35 mL/kg weekly × 18 mo, intensified to twice weekly during 4 relapses	GFR 102 mL/min/1.73 m^2 (2.5 yr)
5	Aberrategui-Garrido et al[31]	18 mo	HE Y1142C, SCR19	442	PE started 4 wk after onset	No; 4 episodes over 22 wk, PE (1st 2 episodes), PI (3rd episode)	ESRD (2.5 mo)
6	De et al[32]	6 mo	HE S1191L, SCR20	147	PI →failure then 10 PE over 2 wk	PI every 2–3 wk × 6.5 yr, intensified to daily PE/PI during 8 relapses	Progressive RI (6.5 yr) ESRD (7.5 yr)

*At initiation of plasmatherapy.
ND, not documented; FH, factor H; Screat, serum creatinine; to convert from μm/L to mg/mL, × 0.0113; PE, plasma exchange; HE, heterozygous; GFR, glomerular filtration rate; PI, plasma infusion; ESRD, end-stage renal disease; RI, renal insufficiency.

PLASMATHERAPY IN PATIENTS WITH *MCP* OR *THBD* MUTATION

Among aHUS patients, those with *MCP* mutations and a pediatric onset of the disease have the best prognosis. These patients have a relapsing course but a risk of ESRD of only 15 to 30% at 5 years follow-up.[1–4] Adult patients, however, seem to have a more frequent evolution to ESRD within the year after onset. The prognosis of *THBD*- HUS is poor, with death or ESRD in 60% of patients.[1,34] Because MCP and THBD are not circulating proteins, a beneficial effect of plasmatherapy is unlikely to be expected in *MCP* or *THBD*-HUS.

Retrospective Series

In the Italian registry, of 35 episodes in 14 patients with *MCP* mutation, 23 were treated (PI 10 to 20 mL/kg and/or PE 30–40 mL/kg, for a total of 2 to 36 treatments in 2 to 6 weeks). Remission (hematologic normalization with or without renal sequel) was observed in 21 of 23 treated episodes and 12 of 12 untreated episodes, confirming that plasmatherapy probably has no benefit in *MCP*-HUS.[2] Also in the French pediatric registry, a favorable outcome was observed in 8 of 9 episodes treated by plasmatherapy (89%) and 15 of 17 untreated episodes (88%).[3]

Case Reports

Treatment modalities and outcome are documented in 24 patients with *MCP* mutation (pediatric onset in 19, adult onset in 5).[35–40] Of 13 patients who received plasmatherapy during all episodes, seven were in ESRD (53%) and 6 had preserved renal function at last follow-up (46%), a proportion similar to that in 11 untreated patients, of whom 5 were in ESRD (45%) and 6 had preserved renal function (55%). However, physicians often choose to perform PE during flares of HUS, to clear up potentially noxious aggregating factors or triggers of endothelial lesions.

A recent publication by Davin et al[40] illustrates that prophylactic PE probably does not influence the outcome in *MCP*-HUS. A boy with *MCP* mutation and HUS at the age of 3 years went into remission after PE. He then received weekly PE for 3.5 years. He had no renal sequelae during 2 years and then developed hypertension, proteinuria, an increase of serum creatinine and LDH, and a decrease of haptoglobin level. Intensification of PE was ineffective, and he was in ESRD 3.5 years after onset.

The response to plasmatherapy is not documented in *THBD*-HUS. Because THBD suppresses not only the complement system but also the coagulation system, its administration as recombinant THBD might be beneficial, as reported in disseminated intravascular coagulation.[41]

PLASMATHERAPY IN PATIENTS WITH *CFI* MUTATIONS

Half of *CFI*-mutated patients go to ESRD within the year after onset, but half recover and have a favorable outcome.[1–4,42] Bienaimé et al recently explained this observation by showing that among 23 patients with *CFI* mutation, 13 had at least one additional genetic risk factor (a mutation in *MCP*, *CFH, C3,* or *CFB*, or a homozygous deletion of the CFH-related protein [*CFHR*]*1*). Ten of these 13 patients presented with ESRD or death within the year after onset. In contrast, none of the patients with isolated *CFI* mutation had a severe initial outcome.[43] Limited information is available about the effect of plasmatherapy in patients with *CFI* mutation, and it is not always known whether the patients had an isolated or combined *CFI* mutation.

Retrospective Series

Among eight episodes in seven patients with *CFI*-aHUS from the Italian registry, six were treated by plasmatherapy. Three of the six treated and one of the two untreated episodes had a partial response to plasmatherapy.[2]

Case Reports

The literature gives information for only five patients treated by PE (patient B in Kavanagh et al,[44] the three patients in Nilsson et al[45]) or PI (patient 7 in Fang et al[38]) at the acute phase. All had complete or partial remission. PE was subsequently maintained in only two patients. All five patients had relapses and all except one (patient 7 in Fang et al[38]) developed ESRD within a few weeks or months. At least three of these five patients have associated genetic anomalies: patient 2 in Nilsson et al[45] had a C3 mutation (patient 16 in Bienaimé et al[43]), patient 3 in Nilsson et al[45] had a homozygous *CFH-R1* deletion and anti-FH antibodies (patient 17 in Bienaimé et al[43]), and patient 7 in Fang et al[38] had a MCP mutation.

PLASMATHERAPY IN PATIENTS WITH *CFB* OR *C3* MUTATIONS

Half of the few patients reported with *C3*[46] or *CFB*[47,48] mutations reached ESRD at first episode or within < 1 year after onset. Of four patients with gain-of-function *CFB* mutation who received PE (patients II7 and III7 of family PER in Goicoechea de Jorge et al[47]) or PI (patient IV2 in Goicoechea de Jorge et al[47] and patient 2 in Roumenina et al[48]), three were plasma sensitive. Two of them (patient III7 on preventive PE and patient IV2 after cessation of PI) had relapses and were in ESRD after 11 years and within a few months, respectively. The third patient had preserved renal function at 18 months follow-up under monthly PI (patient 2 in Roumenina et al[48]). The benefit of plasmatherapy in

patients with a gain of function *C3* mutation is documented in only one patient who had complete remission under PE at first episode. A second course of PE to treat a relapse 14 months later induced hematologic remission but did not rescue renal function.[49] Maybe very frequent PE is necessary in patients with gain-of-function mutations of *CFB* and *C3*, which induce a hyperfunctional C3 convertase.

Guidelines for Plasmatherapy

Recommendations can only be empirical and indicative. Recent guidelines for initial therapy from the European Pediatric Study Group for HUS[50] recommend starting plasmatherapy as early as possible, within 24 hours of presentation. This is justified by the frequent rapid deterioration of renal function in patients with *CFH*, combined *CFI*, *C3,* and *CFB* mutations (and the possibility of anti-CFH antibodies). First-line treatment should be PE, with exchange of 1.5 plasma volume (60 to 75 mL/kg) per session, replaced by FFP. When PE cannot be performed within 24 hours of presentation, PI of 10 to 20 mL/kg should be given if the patient is not volume overloaded and/or hypertensive. PE sessions should be daily for at least 5 days, then five sessions per week for 2 weeks, and then three sessions per week for 2 weeks. Several authors recommend maintaining daily PE until platelet count and LDH level is normalized for several days.[51–53] Some patients require daily PE or PI for long periods. Frequency after the first month should be decided according to which risk factor is demonstrated. The demonstration of *MCP* mutation allows withdrawal of plasmatherapy. For patients with *CFH*, *CFI*, *C3*, *CFB* mutations, and those with unexplained (no mutation, no anti-FH antibodies) but plasma-sensitive HUS, the possibility to switch from PE to PI, and the maximal interval of time between two sessions need to be determined individually. Plasmatherapy should probably never be stopped in patients with a *CFH* mutation, and probably also *CFI* combined mutation, *CFB,* or *C3* mutation. However, an attempt to withdraw plasmatherapy is generally considered in the few patients without any manifestation of HUS despite tapering PE/PI to monthly or less than monthly sessions for several months or years.

THE LIMITS OF LONG-TERM PLASMATHERAPY

Practical problems may limit the feasibility of PE over the long term. First, PE requires a technically trained center, especially for young children.[54,55] Second, a central venous catheter similar to those used for hemodialysis is necessary if the patient has no arteriovenous fistula. This is associated with the risk of central venous thrombosis, especially in young children, and infection. Third, some patients develop anaphylactic reactions to FFP, which may require cessation of any form of plasmatherapy. Fourth, as noted earlier, it is uncertain whether the beneficial effect of plasma therapy can persist for decades.

CONCLUSION

Today, plasmatherapy remains the first-line treatment in aHUS. However, complement blockers are now available, and several case reports show that one of them, eculizumab, an anti-C5 monoclonal antibody, can replace plasmatherapy in plasma-sensitive patients[56,57] and control the disease in plasma-resistant patients.[58,59] Prospective trials with eculizumab are presently ongoing. FH concentrate should also be available for therapeutic trials in the years to come, and recombinant FH possibly some day. We hope these new therapeutics will offer patients a better chance of preserved renal function and a better quality of life.

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